PROMETHEUS UNHEALED! HEPATOCELLULAR CARCINOMA

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Disclosures

- None

10 Leading causes of death by age group, South Dakota, 2013-2017

	Age Groups											
	<1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+	Total
Rank	Total 395	Total 87	Total 136	Total 520	Total 670	Total 1021	Total 2,126	Total 4,349	Total 6,065	Total 8,792	Total 13,951	Total 38,112
1	Conditions originating in perinatal period 155	Accidents 36	Accidents 54	Accidents 234	Accidents 252	Accidents 218	Cancer 511	Cancer 1,460	Cancer 2,083	Cancer 2,315	Heart disease 3,744	Heart disease 8,462
2	Congenital abnormalities 94	Homicide 12	Suicide 22	Suicide 172	Suicide 143	Suicides 138	Heart disease 369	Heart disease 948	Heart disease 1,322	Heart disease 1,902	Cancer 1,724	Cancer 8,290
3	Accidents 44	Congenital abnormalities 8	Cancer 12	Homicide 31	Liver disease 42	Heart disease 130	Accidents 248	Accidents 267	Chronic lower respiratory diseases 499	Chronic lower respiratory diseases 740	Alzheimer's disease 1,582	Accidents 2,390
4	SIDS 34	Cancer 6	Homicide 9	Cancer 22	Heart disease 33	Cancer 125	Liver disease 182	Chronic lower respiratory diseases 209	Diabetes 252	Stroke 515	Stroke 1,114	Chronic lower respiratory diseases 2,285
5	Unknown causes 21	Influenza & pneumonia 3	Congenital abnormalities 6	Heart disease 10	Homicide 33	Liver disease 121	Suicide 145	Diabetes 199	Stroke 220	Alzheimer's disease 478	Chronic lower respiratory diseases 785	Alzheimer's disease 2,167
6	Homicide 9	Other viral diseases 2	Other metabolic disorders 3	Undetermined intent 5	Cancer 31	Diabetes 46	Diabetes 82	Liver Disease 181	Accidents 182	Accidents 315	Influenza & pneumonia 571	Stroke 2,064
7	Other metabolic disorders 6	Other disorders of nervous system 2	Heart disease 3	Episodic & paroxysmal disorders 4	Diabetes 14	Homicide 24	Stroke 57	Stroke 129	Liver Disease 105	Diabetes 303	Accidents 540	Diabetes 1,259
8	Influenza & pneumonia 6	Bronchitis 2	Cerebral Palsy 3	Legal intervention 4	Episodic & paroxysmal disorders 10	Stroke 17	Chronic lower respiratory diseases 44	Suicide 106	Influenza & pneumonia 103	Influenza & pneumonia 193	Unspecified dementia 423	Influenza & pneumonia 991
9	Other viral diseases 3	Undetermined intent 2		Ill-defined and unknown causes 4	Influenza & pneumonia 9	Septicemia 16	Influenza & pneumonia 40	Septicemia 66	Alzheimer's disease 86	Parkinson's disease 171	Diabetes 361	Suicide 814
10	Stroke 3	Ill-defined and unknown causes 2		Cerebral Palsy 4	Stroke 7	Mental & behavioral disorders due to alcohol 16	Mental & behavioral disorders due to alcohol 39	Influenza & pneumonia 52	Kidney disease 73	Septicemia 121	Hypertension 297	Liver disease 695
11	Undetermined intent 3				Pregnancy & childbirth 7					Unspecified dementia 121		
	All other 17	All other 12	All other 24	All other 30	All other 89	All other 170	All other 409	All other 732	All other 1,140	All other 1,613	All other 2,810	All other 8,695

Top 5 causes of death are highlighted.

Source: South Dakota Vital Statistics Reports, 2013-2017

Case Description

- 55 year old Caucasian male office worker was evaluated by his new PCP for elevated LFT's >15 years.

Case Description

- Past Medical History :
  - Hypertension, Type 2 DM, Obesity, High TG's and Elevated LFT's for>15 years.
- Medications :
  - Antihypertensive, Fibrates, hypoglycemic agent
- Social History :
  - A glass of wine every 6 months, no tattoos , denies IVDU & high risk sexual activity.
- Family History :
  - No liver disease, CAD,DM.

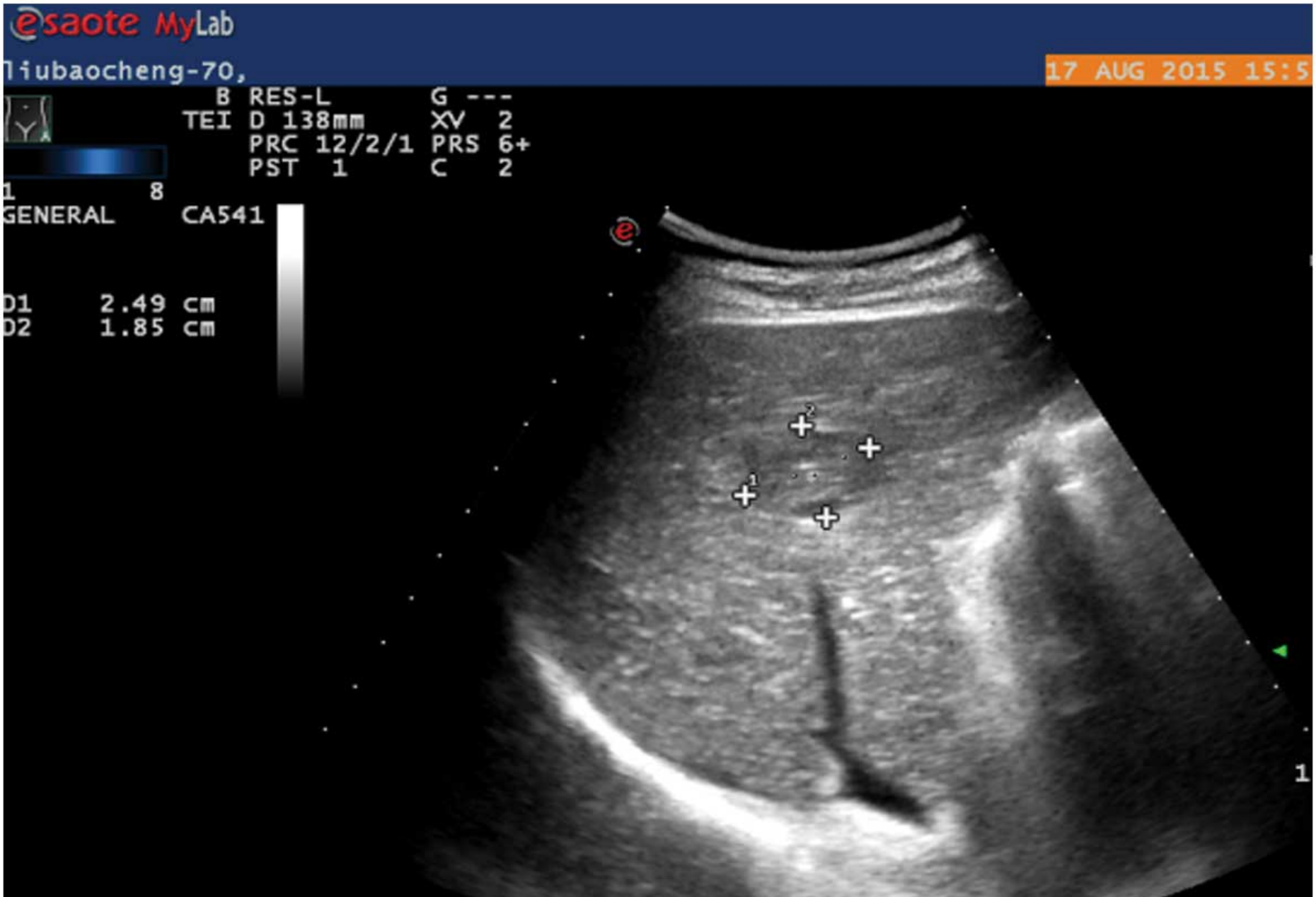
Case Description

- Physical Exam :

  Obese 200lbs,5 ft. 2 inches, BMI 36.9,Waist circumference 107

  - Oriented x3 ,Pedal edema, Vascular spider on his chest. Rest of the exam normal.

  - Pertinent Labs:
  - Anemic ,platelets 130,AST/ALT: 88/56,normal bilirubin, low albumin, high total protein, INR 1.1
  - Viral Serologies: Negative
  - Serum antibodies : Negative.
  - Transferrin saturation :36%


esaote MyLab
liubaocheng-70,
17 AUG 2015 15:5
B RES-L G ---
TEI D 138mm XV 2
PRC 12/2/1 PRS 6+
PST 1 C 2
1 8
GENERAL CA541
D1 2.49 cm
D2 1.85 cm
1

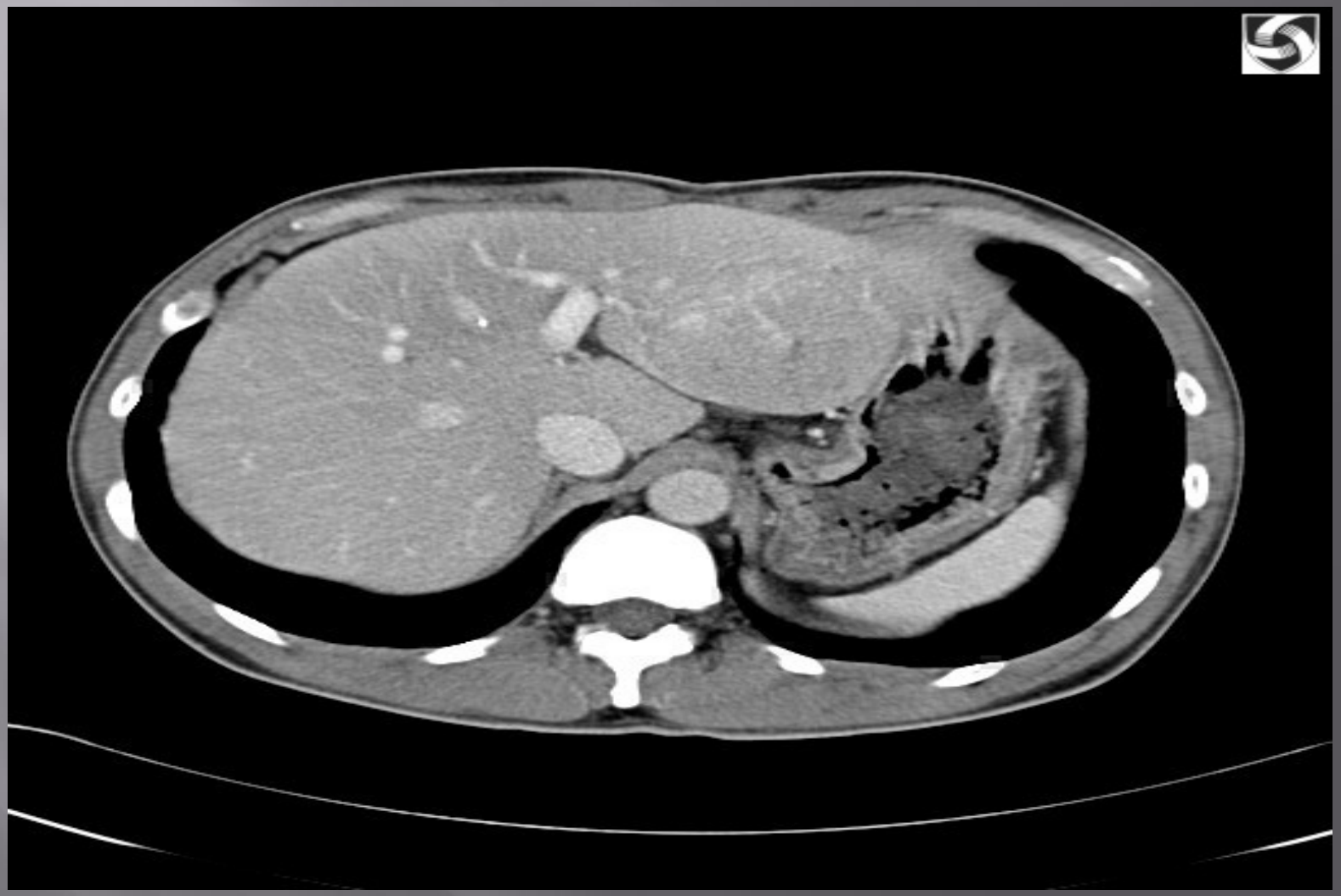
HCC Background Imaging

Early arterial phase. A heterogeneously enhancing mass, approximately 4-5 cm in size, is visible in the liver.

HCC Background Imaging

Late-arterial phase image demonstrates additional enhancement of the mass

HCC Background Imaging



Portal venous phase shows decreased image enhancement

HCC Outline

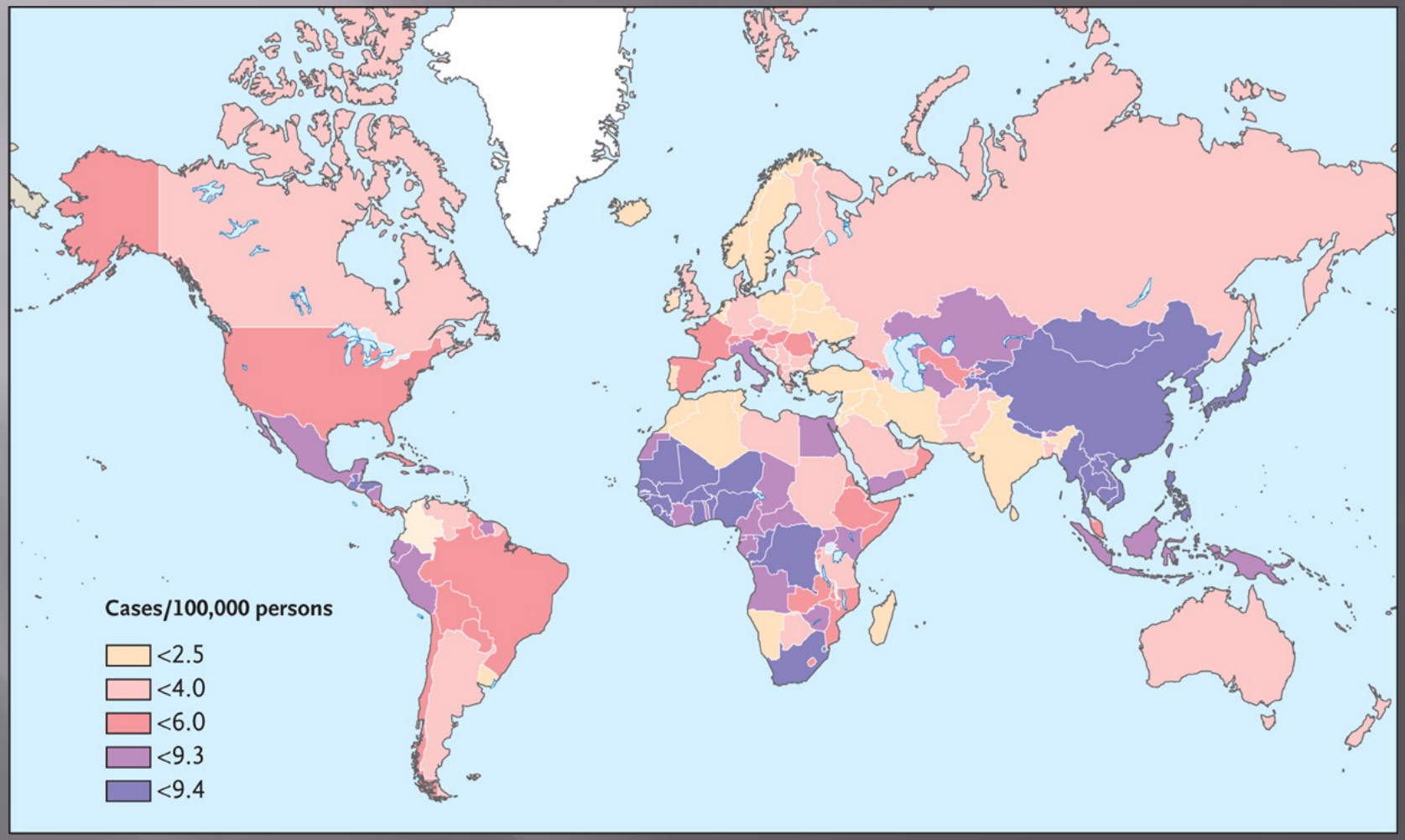
- Epidemiology
- Etiology/Risk Factors
- Clinical Features
- Surveillance
- Diagnosis
- Treatment

EPIDEMIOLOGY

HCC Background Statistics

- HCC is the most rapidly increasing cause of cancer death in the US and the fifth most common cancer worldwide.
- Second leading cause of cancer related death.
- Leading cause of mortality among patients with cirrhosis.
- Characterized by aggressive tumor behavior and poor prognosis.

Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.



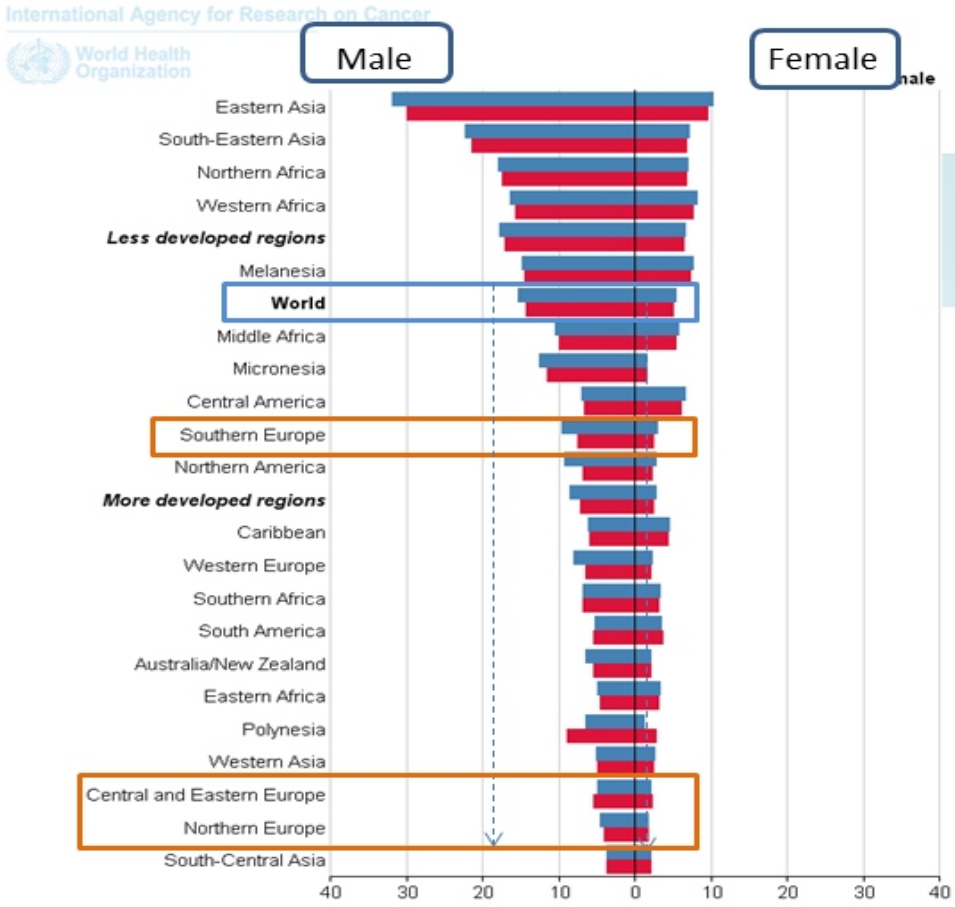
HCC: Demographics

- Gender M>F
- Race
- Age

SEER DATABASE

HCC: Incidence

Worldwide estimated new PLC cases and deaths



Demographic risk factors:
- male gender
- geographic area

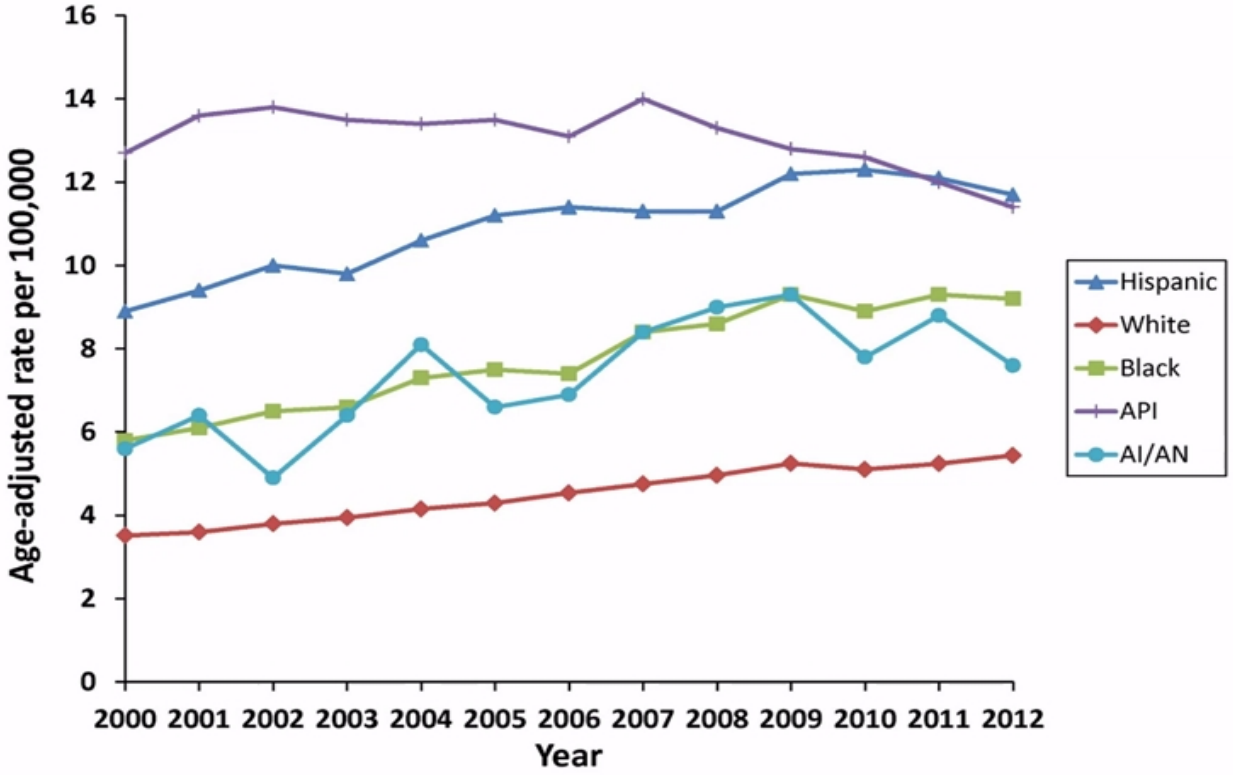
Incidence Mortality

I:M ratio = 1.05

Globocan, IARC 2012

HCC: Incidence

Age-adjusted HCC incidence rates in the United States between 2000 and 2012



Gastroenterology 2017 152, 812-820.e5DOI: (10.1053/j.gastro.2016.11.020)

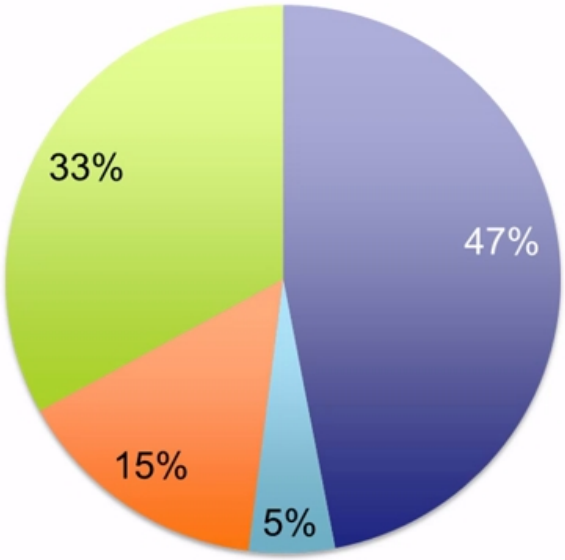
HCC:Risk Factors

- Cirrhosis : HBV, HCV, NASH, Alcohol etc.
- Infections :Hepatitis B virus
- Behavioral factors : (Alcohol)
- Obesity
- Others :Aflatoxins. Mycotoxin. Pesticides

Liver cancer burden varies markedly by sex and geographic region due to risk factor exposure

HCC:Risk Factors

HCV is the Dominant Risk Factors for HCC in the United States



(N=691)

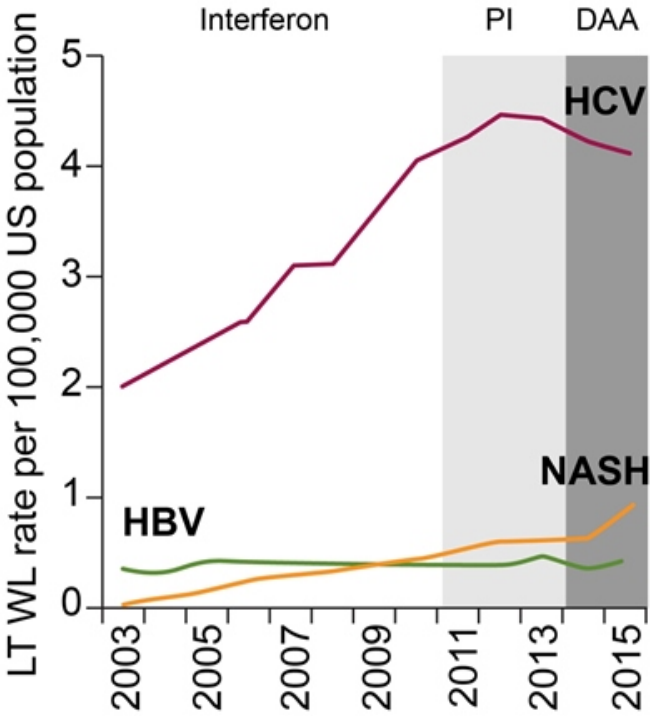
- HCV
- Both
- HBV
- Neither

- HBV most frequent in Asians
- HCV most frequent in whites and blacks

HCC: Risk Factors

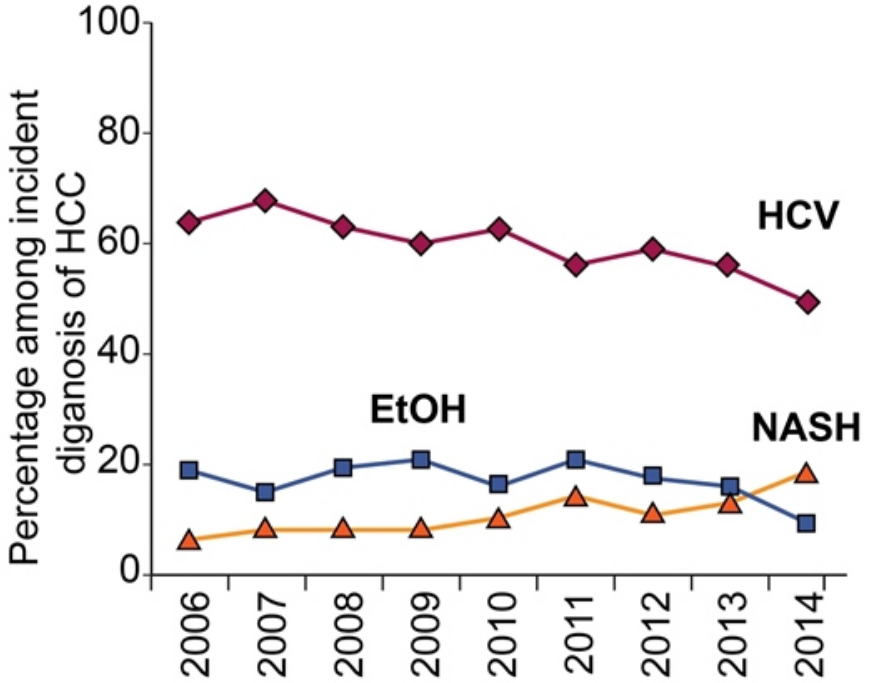
NAFLD as a risk factor for HCC

Scientific Registry of Transplant Recipients database.



Flemming *et al.* Hepatology 2017

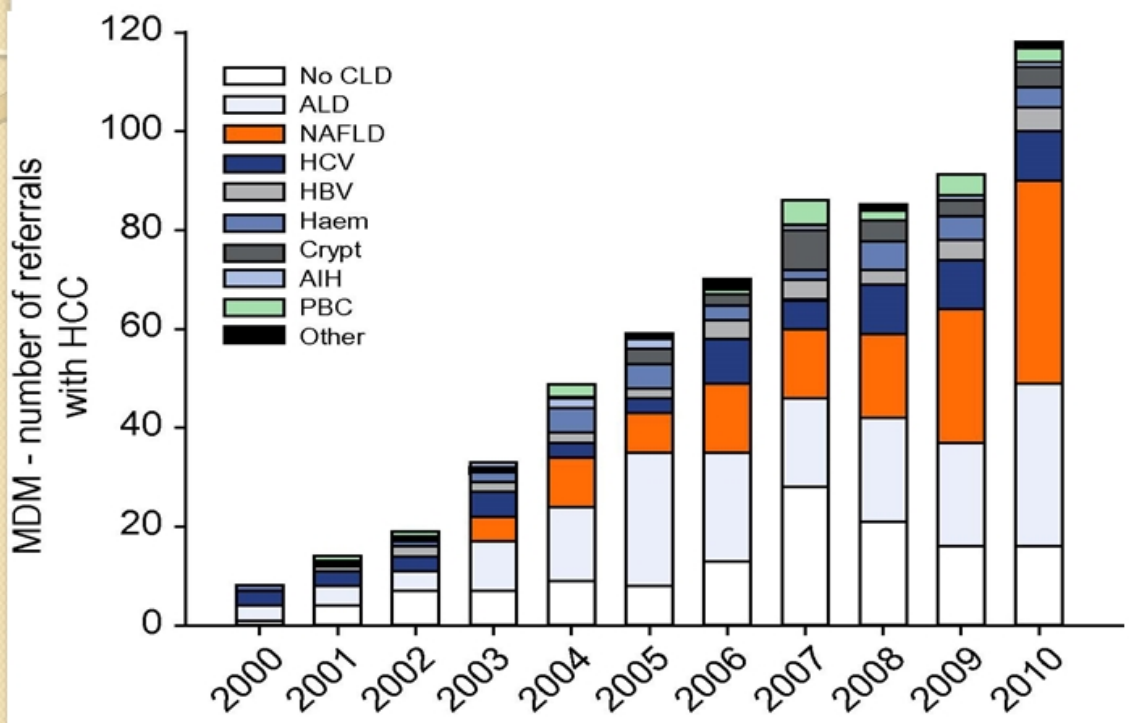
Diagnosis distribution among incident HCC in HealthCore



Goldberg *et al.* Gastroenterology 2017

HCC: Incidence

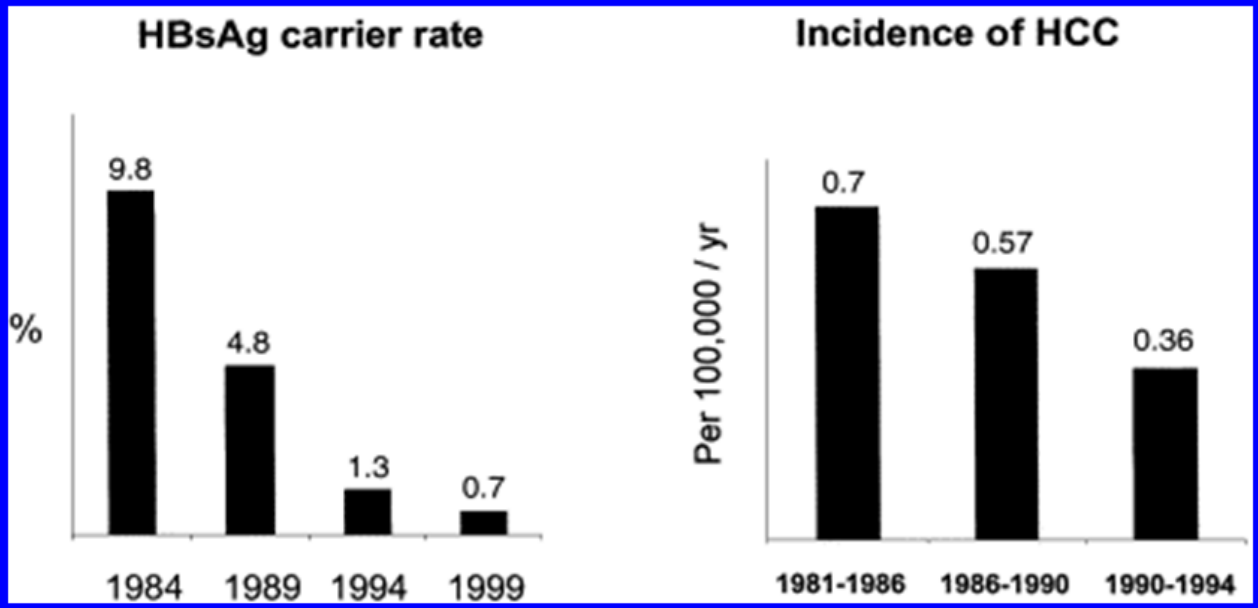
NAFLD is now the commonest cause of HCC in the North East UK



Patients with NAFLD associated HCC had a higher incidental presentation (38.2%) and lower prevalence of cirrhosis (77.2%).

HCC: Impact of Vaccination

Impact Of Universal Vaccination On HBV Infection & HCC In Taiwanese Children

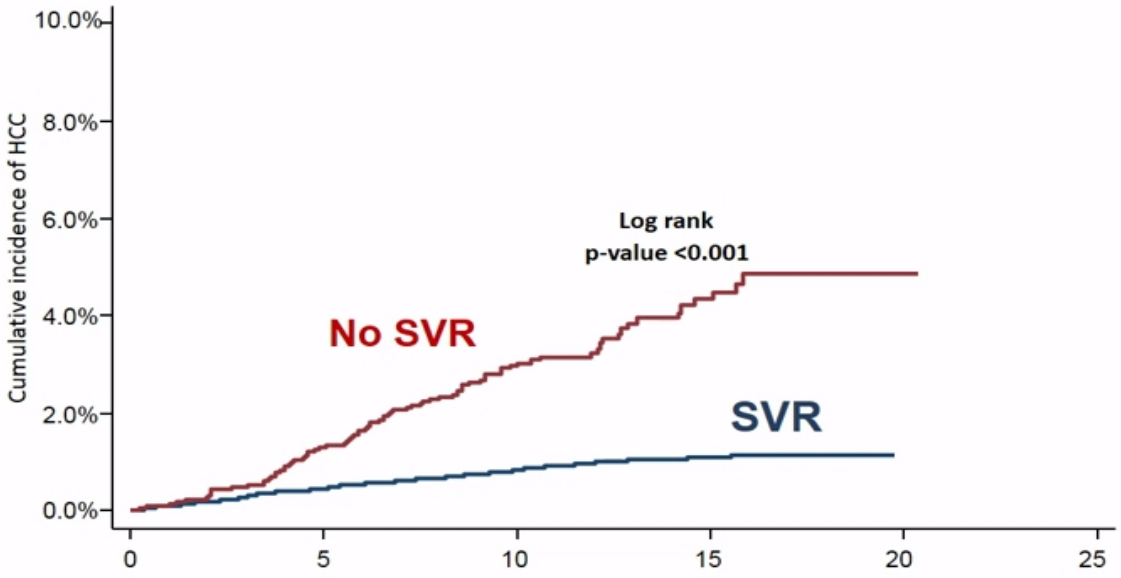


From: Chang MH et al., N Engl J Med. 1997 Jun 26;336(26):1855-9.

HCC: Incidence

HCC after DAA-induced SVR

Cumulative HCC incidence rates by SVR



N at risk (N HCC)											
SVR	19518	(85)	19372	(68)	14364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

CLINICAL FEATURES

Symptoms

- RUQ pain.
- Weight Loss.
- Decompensation in a Cirrhotic.
- Obstructive jaundice.
- Intraperitoneal bleeding (tumor rupture).
- Fever.

Signs

- Reflect underlying liver disease.
- Manifestations of paraneoplastic Syndromes.

Paraneoplastic phenomena

- Dermatomyositis

Pemphigus foliaceus

Porphyria cutanea tada

Paraneoplastic Syndromes

- Hypoglycemia
- Erythrocytosis
- Hypercalcemia
- Diarrhea.

Metastases

- Found ~10 % of patients at diagnosis.
- Patterns of spread:

  -Lung

  -Intraabdominal LN.

  -Bone.

  -Brain.

  -Adrenal gland.

SURVEILLANCE

Reduce Mortality

Improve survival

Detect early stage curative HCC

SURVEILLANCE

- Cirrhosis from any cause The prevalence of cirrhosis among patients with HCC has been estimated to be 85%-95%.
- Hepatitis B carriers A randomized surveillance study performed in HBV carriers, showed a 37% reduction in mortality for those who underwent surveillance.

AASLD

SURVEILLANCE

- **Hepatitis B carriers**

-Asian males 40 years

-Asian females 50 years

-Hepatitis B carriers with family history of HCC

Other Cirrhosis

-HCV Cirrhosis

-Stage 4 PBC

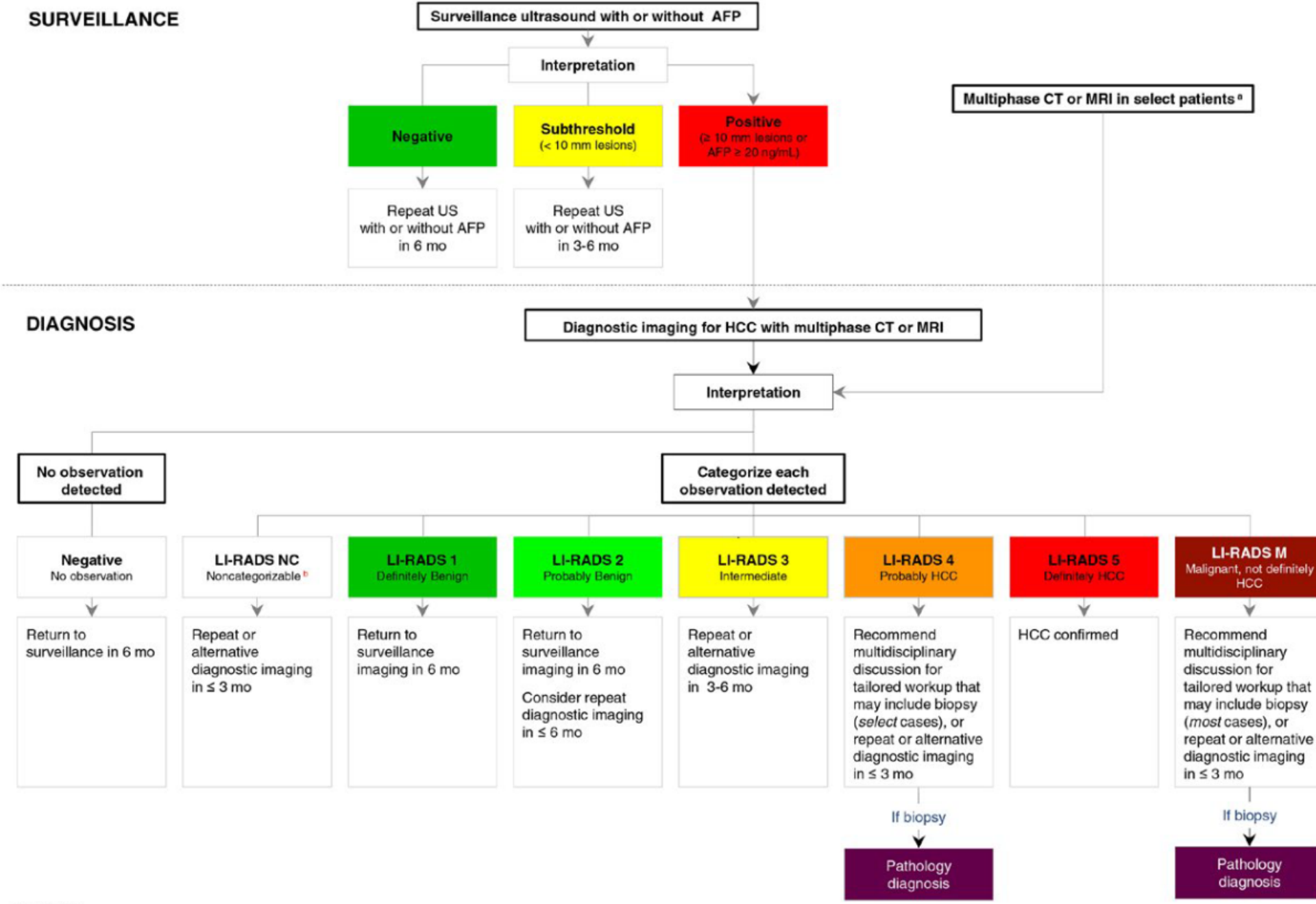
-Genetic Hemochromatosis and cirrhosis

-A1AT Deficiency and cirrhosis

Modes of Surveillance

- Surveillance for HCC should be performed using ultrasonography with or without Alpha-fetoprotein-AFP.
- Patients should be screened at 6 month intervals

DIAGNOSIS



Footnotes

a. Multiphase CT or MRI in select patients — Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list and other factors).

STAGING, PROGNOSIS AND MANAGEMENT

Staging

Staging helps in:

-Prognosis

-Choice of therapy with greatest survival potential.

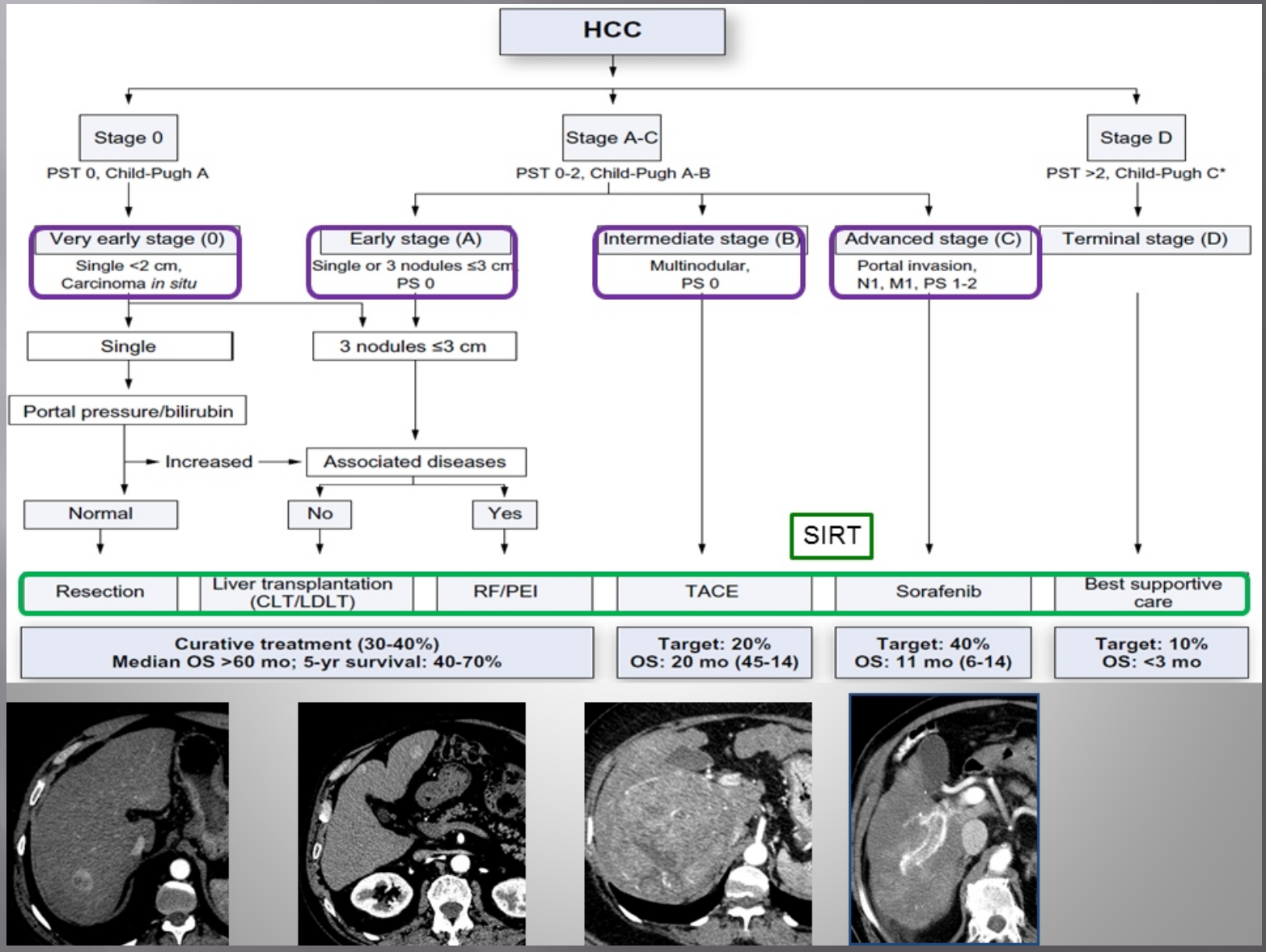
Prognosis is complicated in HCC patients as the underlying liver function also affects outcome.

Staging

It is recommended that the staging system takes into account tumor stage, liver function and prognosis(Child Pugh, MELD) and physical status.

- BCLC- Barcelona Clinic Liver Cancer is the only staging system that accomplishes these aims.

Staging


HCC
Stage 0
PST 0, Child-Pugh A
Stage A-C
PST 0-2, Child-Pugh A-B
Stage D
PST >2, Child-Pugh C*
Very early stage (0)
Single <2 cm,
Carcinoma in situ
Early stage (A)
Single or 3 nodules ≤3 cm
PS 0
Intermediate stage (B)
Multinodular,
PS 0
Advanced stage (C)
Portal invasion,
N1, M1, PS 1-2
Terminal stage (D)
Single
3 nodules ≤3 cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
SIRT
Resection
Liver transplantation (CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive care
Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%
Target: 20%
OS: 20 mo (45-14)
Target: 40%
OS: 11 mo (6-14)
Target: 10%
OS: <3 mo

PROGNOSIS

Child Pugh Class

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85 percent; class B: 80 and 60 percent; and class C: 45 and 35 percent.

INR: international normalized ratio.

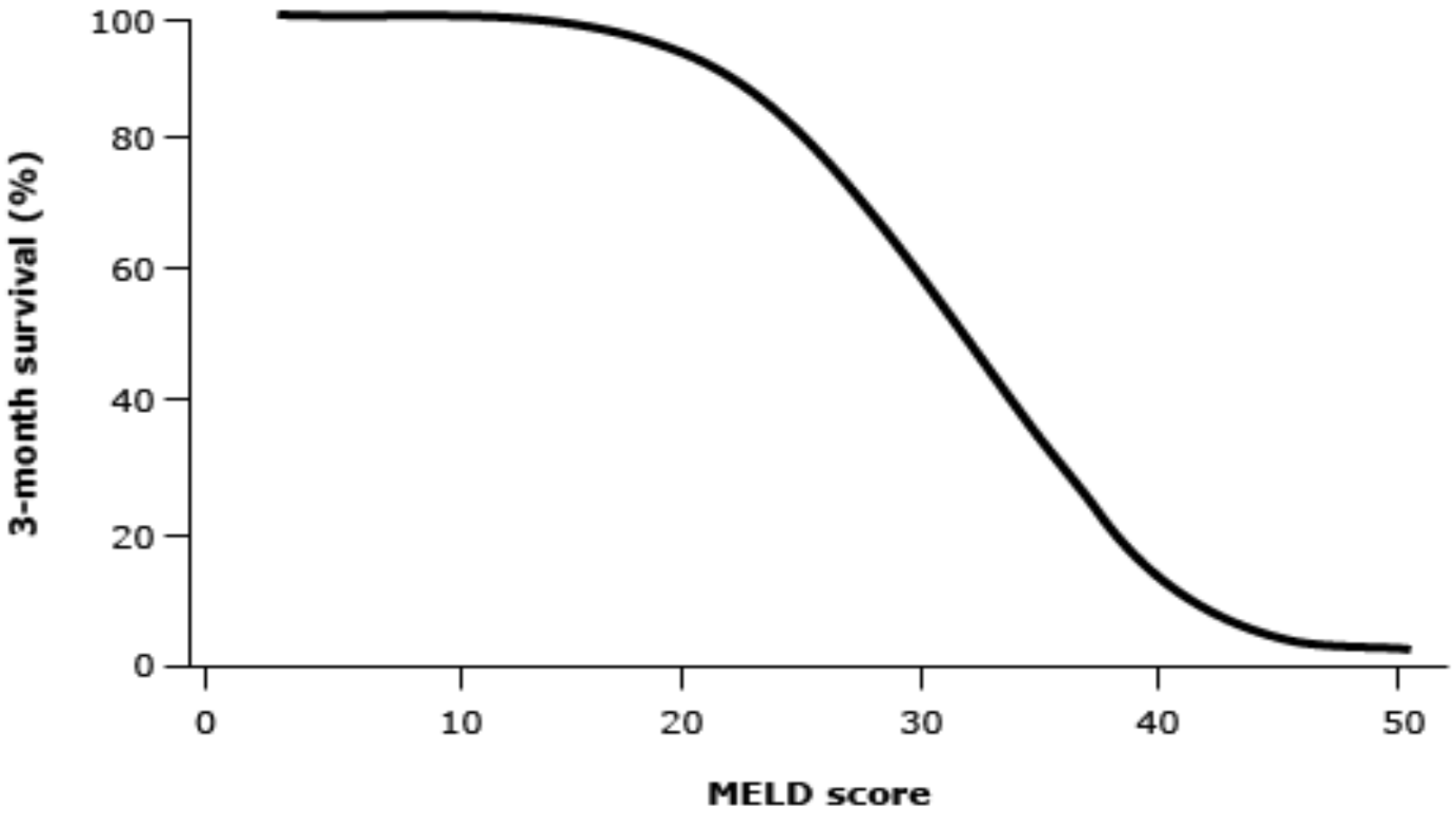
UpToDate®

MELD SCORE

- The MELD score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for bilirubin, creatinine, INR and sodium to predict three-month survival.

- HCC within Milan Criteria is assigned a MELD of 22 with a 10% increase every 3 months.

Estimated 3-month survival as a function of the MELD score in patients with cirrhosis



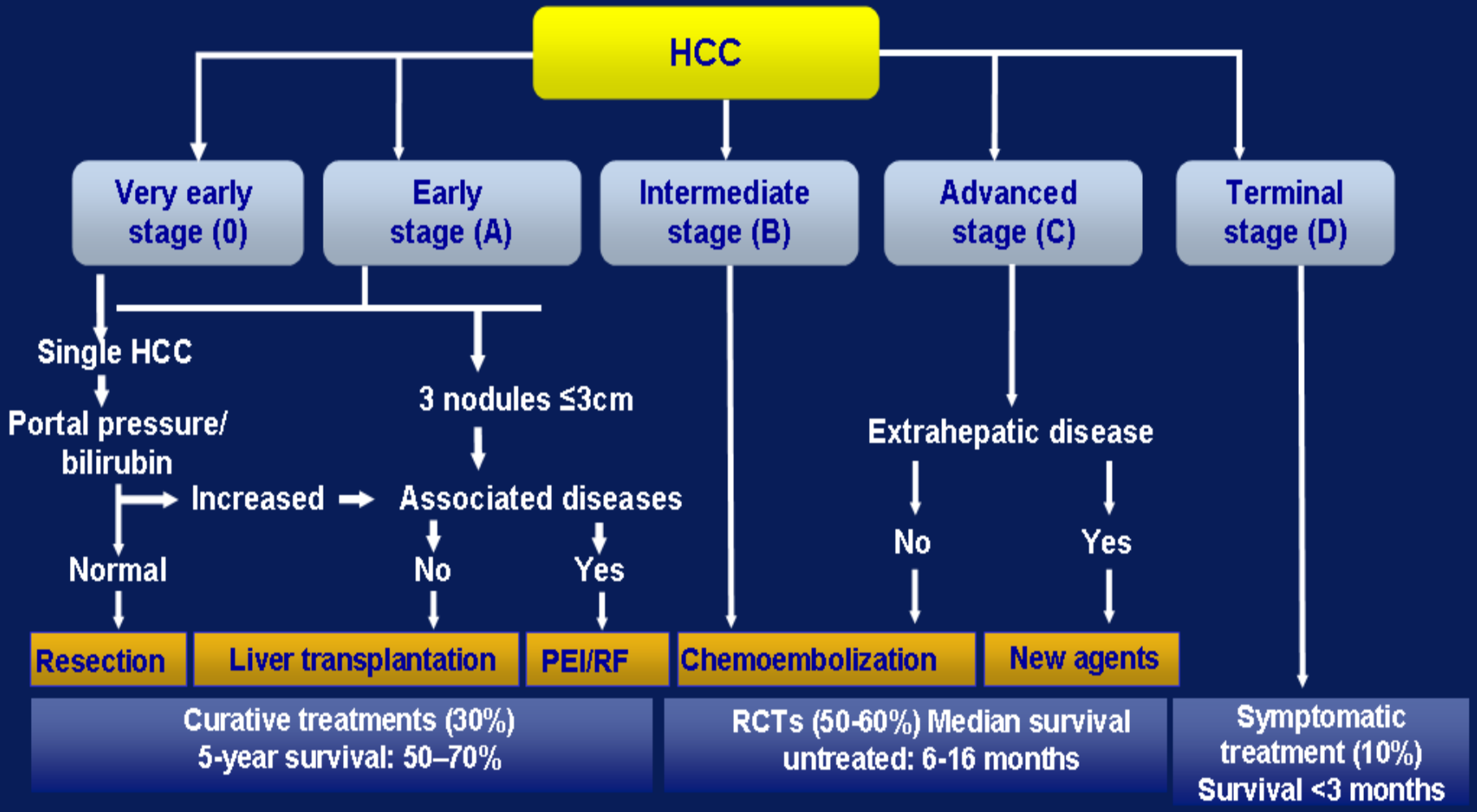
MELD: Model for End-Stage Liver Disease.

Adapted from: Wiesner, R, Edwards, E, Freeman, R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124:91.

MANAGEMENT

Multidisciplinary approach involving Hepatologists, Pathologists, Radiologists, Surgeons and Oncologists.

BCLC Staging and Treatment Strategy



Adapted from Llovet JM, et al, Lancet 2003;362:1907–17

LIVER TRANSPLANTATION FOR HCC

- Simultaneously cure's the tumor and the underlying cirrhosis.
- Confined to single lesion ≤5 cm, up to three lesions, <= 3 cm, no gross vascular invasion, and no metastases-Milan Criteria.
- 75%,4yr survival.

Organ Allocation

- UNOS -United Network for Organ Sharing allocates livers on the basis of MELD score.
- Most HCC patients have minimal liver dysfunction leading to increased waiting time and subsequent tumor progression beyond Milan criteria.
- A priority system exists for HCC .

RESECTION FOR HCC

- Patients with preserved liver function, no vascular invasion no evidence of p. hypertension.
- Best outcome in Child Pugh A.
- Perioperative mortality 1-3%
- 5yr survival ~70- 90%
- Recurrence-70% at 5 years

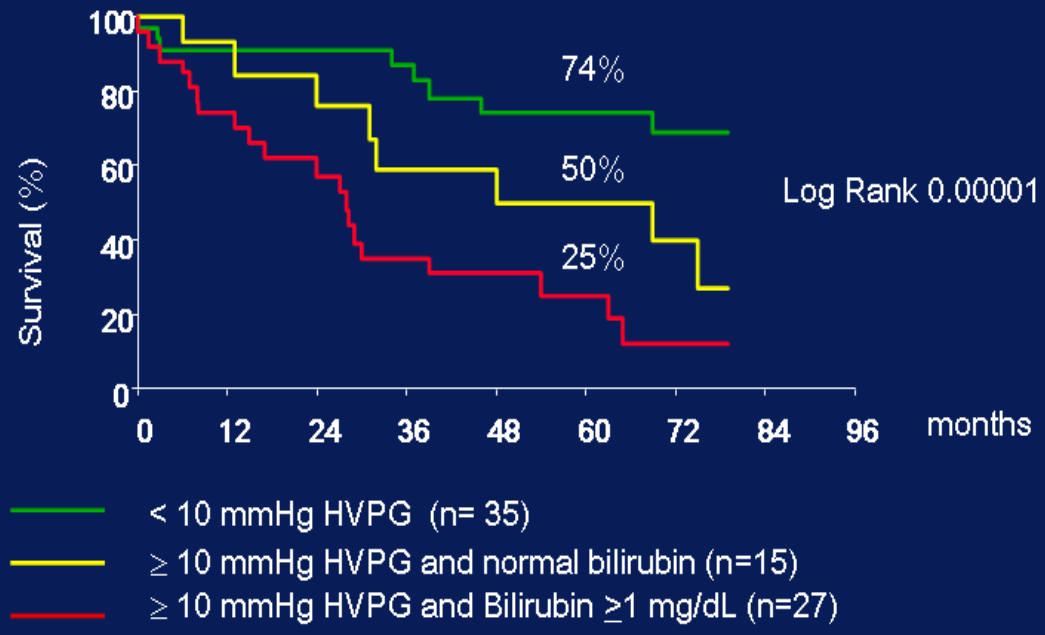
RESECTION FOR HCC

Survival after Surgical Resection for Hepatocellular Carcinoma

Best candidates for resection : Solitary HCC ≤ 5 cm

Child-Pugh A: Low portal hypertension

Normal bilirubin



Llovet JM et al. Hepatology 1999;30:1434-40

Loco regional Therapies

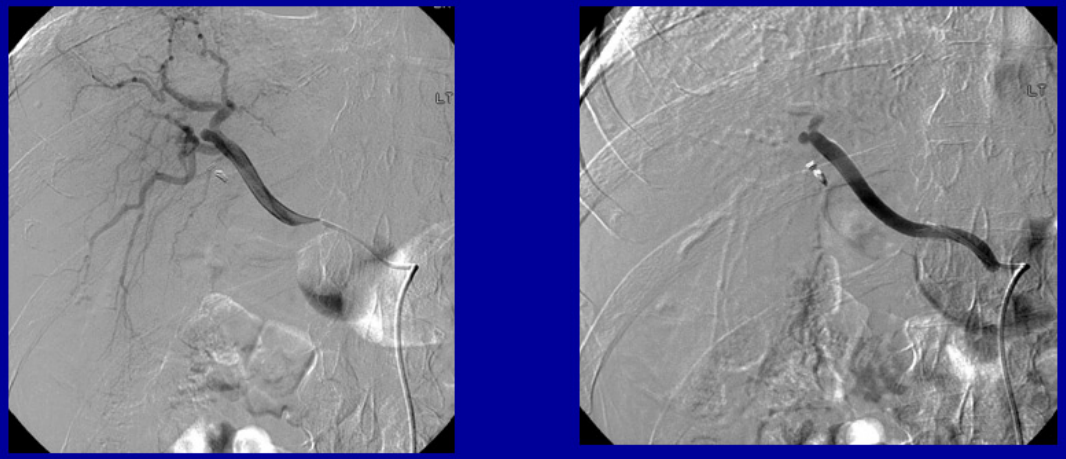
- Trans arterial Chemoembolization –TACE
- Radiofrequency Ablation
- Percutaneous Ethanol Injection
- Systemic Chemotherapy
- Yttrium Radio embolization

Trans arterial Chemoembolization –TACE

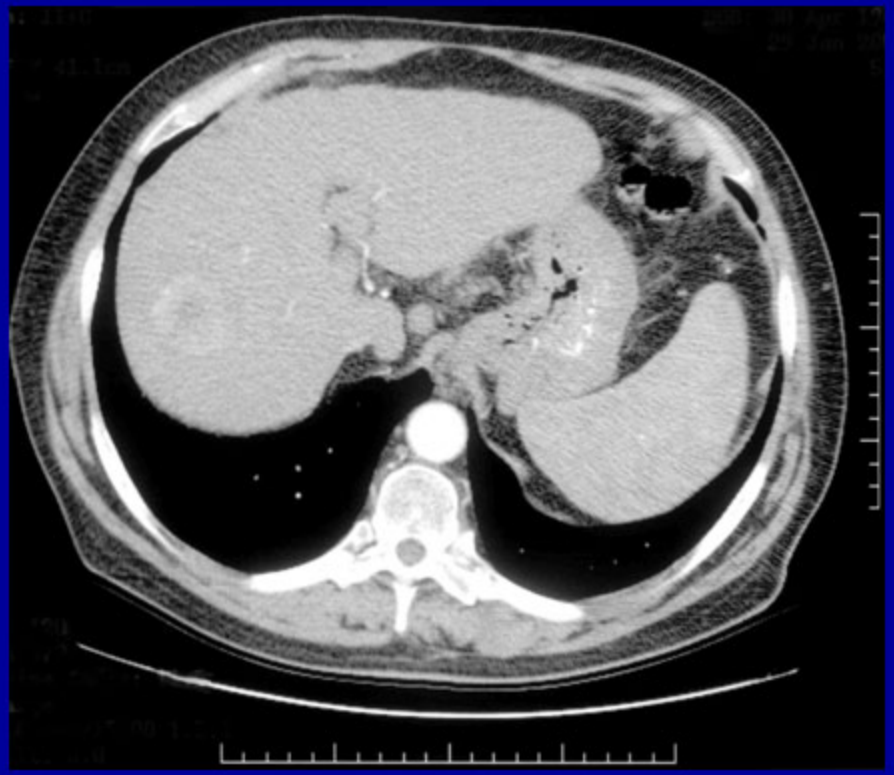
- Injection of anticancer drugs into the hepatic artery followed by embolizing beads.

Transarterial chemoembolization

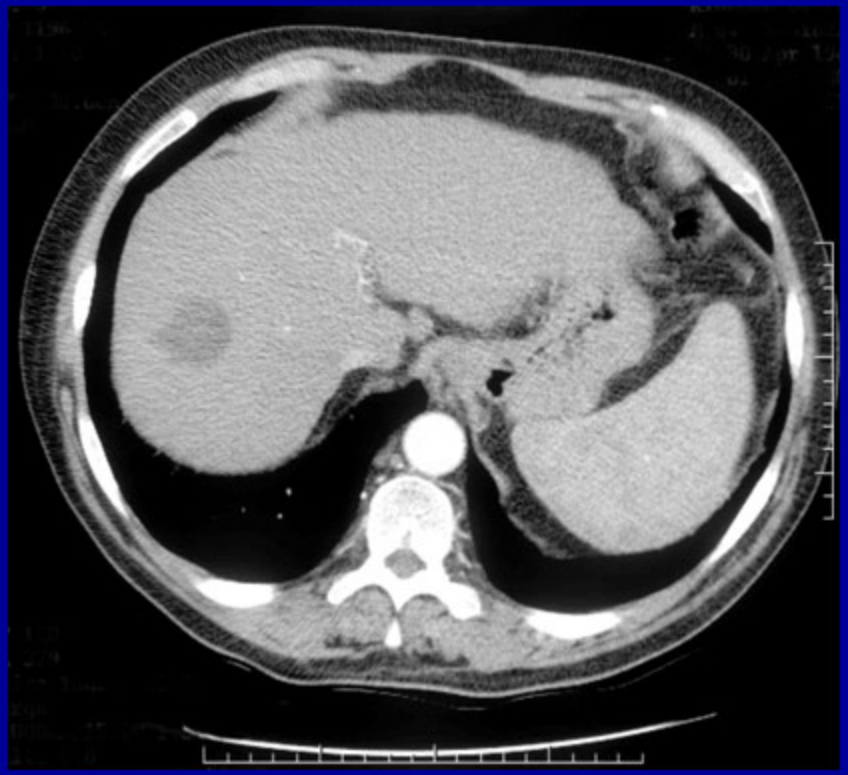
TACE



ASSESSMENT OF TUMOUR RESPONSE TO TACE



pre treatment
AFP 1824



post treatment
AFP 99

Stable disease by RECIST Complete response by EASL criteria

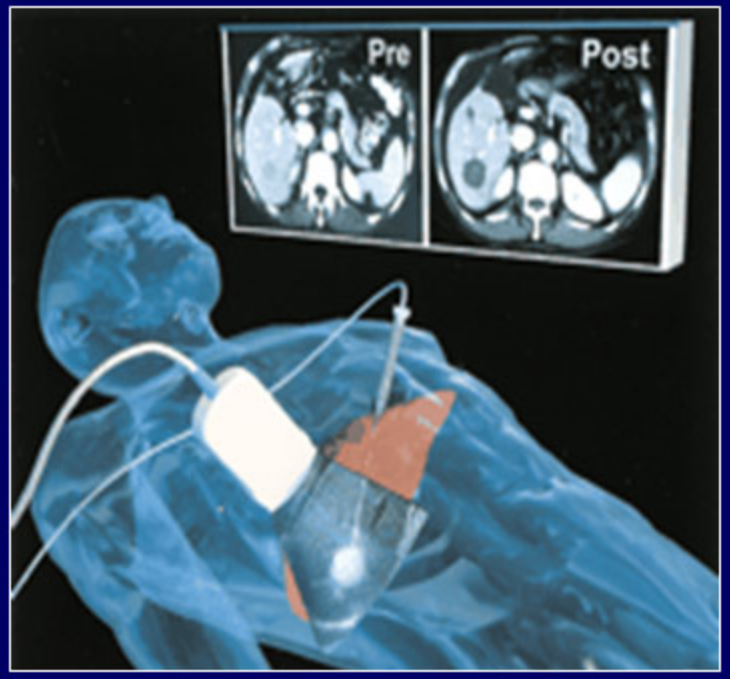
RADIOFREQUENCY ABLATION

- Tumor necrosis using thermal energy.

- Patients who do not meet resectability criteria.
- Best response <4 cm tumors

- Not used in tumors along the dome and inferior edge of liver and in the neighborhood of a vessel.
- Local recurrence 0-28%.

Percutaneous Ablation: New Methods



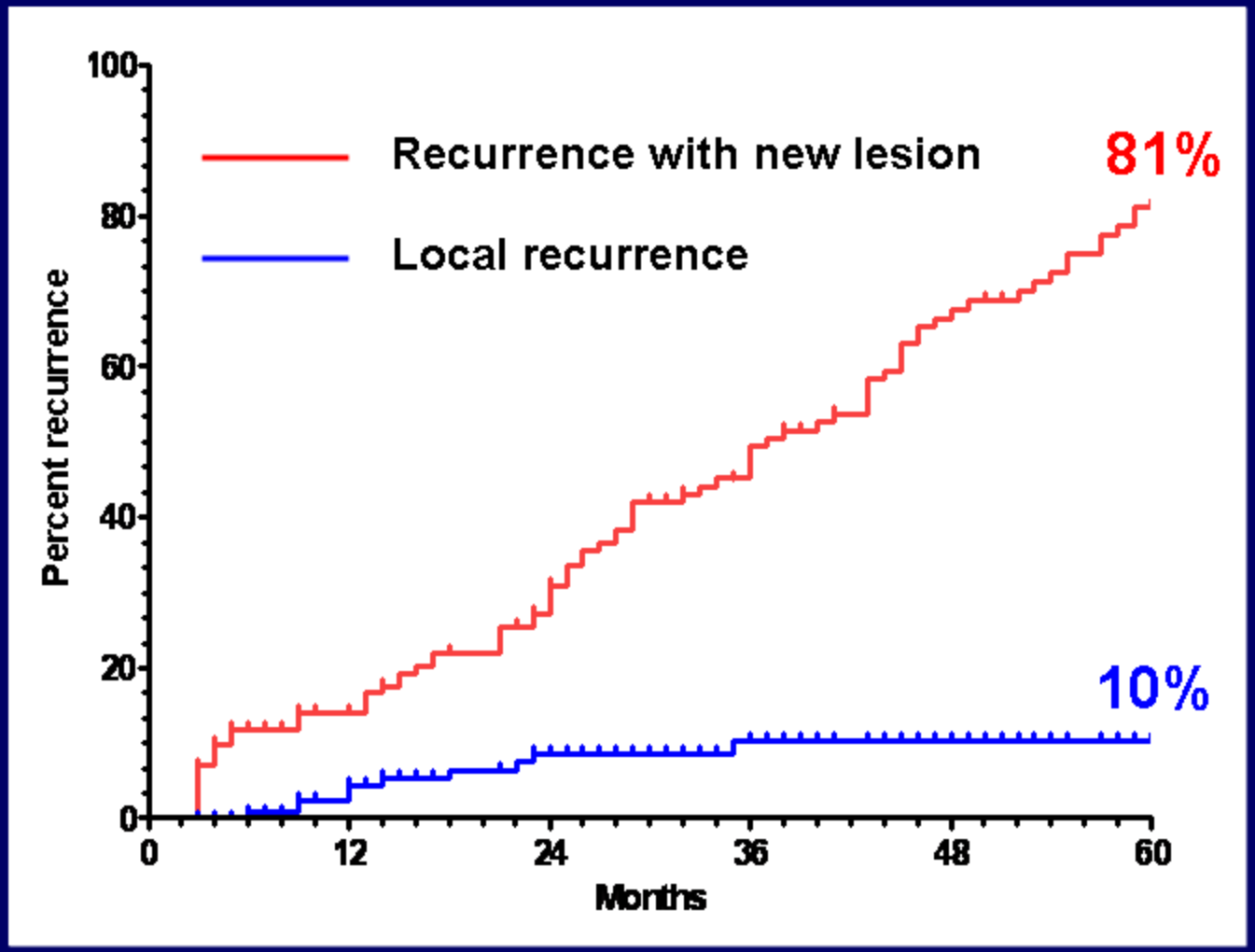
- Laser ablation
- Microwave ablation
- Cryoablation
- High-focused ultrasound
- Radiofrequency ablation

High-power generators

Multitined electrodes

Perfusion electrodes

RFA - Early HCC: Long-Term Outcomes



Lencioni R et al, Radiology 2005

Systemic Chemotherapy

Molecularly targeted therapy

Sorafenib (Nexavar)

multitargeted tyrosine kinase inhibitor

FUTURE DIRECTIONS

Other nonsurgical modalities

Radiotherapy
Radioembolization
Cryotherapy

THANK YOU

?Questions