HCC personalised treatment

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Dutch Liver Week 2017

Disclosure belangen R.A. de Man

Disclosure belangen spreker

Spreker – Gilead, Norgine.
Onderwijs – Virology International
Two hands Events.
Onderzoek – Biotest Pharma,ISA,MLDS

De presentatie bevat verwijzingen naar in Nederland nog niet voor die indicatie geregistreerde geneesmiddelen.

Overzicht

- Welke vragen stelt de patient zich ?
- Welke vragen stelt de arts zich ?
- Epidemiologie en risicofactoren
- Diagnose
- Management en prognose
- Conclusies

Erasmus MC

Aanloop naar een hepatocellulair carcinoom

- Patiënt heeft een klacht, symptoom of lab. afwijking
- Echografie buik/lever
- Haardvormige afwijking gevonden

- Die vervolgens een nieuw probleem creëert in plaats van een bestaand probleem op te lossen
- Dat nieuwe probleem geeft aanleiding tot extra onderzoek (CT, MRI)

- En dan zie ik de patiënt op mijn spreekuur……

Erasmus MC

Kernvragen voor de patiënt

1. Is het kanker ?
2. Is er iets aan te doen ?
3. Kan ik morgen antwoord op mijn vragen hebben ?
4. Ben ik op de juiste plaats om deze vragen te beantwoorden ?

Erasmus MC

Kernvragen voor de patiënt

Vertaald in het proces

1. Duidelijk antwoord op de vraag
2. Consequentie van de bevinding
3. Snelheid
4. Kwaliteit van zorg
5. Beschikbaarheid van de moderne behandelopties

Erasmus MC

Kernvragen voor de arts

1. Is er een leverziekte ?

2. Is er wel een haardvormige afwijking ?

3. Waar zit die afwijking precies ?

4. Wat voor eigenschappen (solide of cysteus) ?

Erasmus MC

Kernvragen voor de arts

5. Werkdiagnose afwijking

6. Plan van aanpak

7. Zelf doen, patiënt verwijzen of beeldmateriaal verwijzen ?

Erasmus MC

Therapie Hepatocellulair carcinoom
toenemende multimodaliteit benadering

Chirurgie

- Gedeeltelijke leverresectie met of zonder v.porta embolisatie
- Volledige leverresectie en levertransplantatie
- Open RFA

Interventie radiologie

- Gesloten RFA/MWA
- Chemoembolisatie (TACE)
- Radioembolisatie (TARE)
- (Percutane Ethanol injectie)

Protocollair

- Stereotactische Radiotherapie
- Systemische therapie

Erasmus MC

Teaching Aims

- Understand the difference between the diagnostic work-up of a nodule in liver cirrhosis and non-cirrhotic liver disease.
- Therapy selection in HCC depends on
  - extent of liver disease
  - extent of tumor burden
  - performance status of the patient
  - patient preference
  - (available treatment modalities in center)
- Systematic approach using guidelines:
  - IKNL www.oncoline, AASLD, EASL, LIRADS, BCLC

Patient 1: history

- Male patient, 56 years.
- Diagnosed 1982 chronic HBV HBeAg(-), Stage CPH
- Mother, sister chronic HBV infection.
- Mother died of HCC.

- 1982-2004: no antiviral therapy; “multiple flares”
- 1988: biopsy CAH with fibrosis

- Referred to hepatologist in 2004: how to proceed ?

Patient 1: 2004

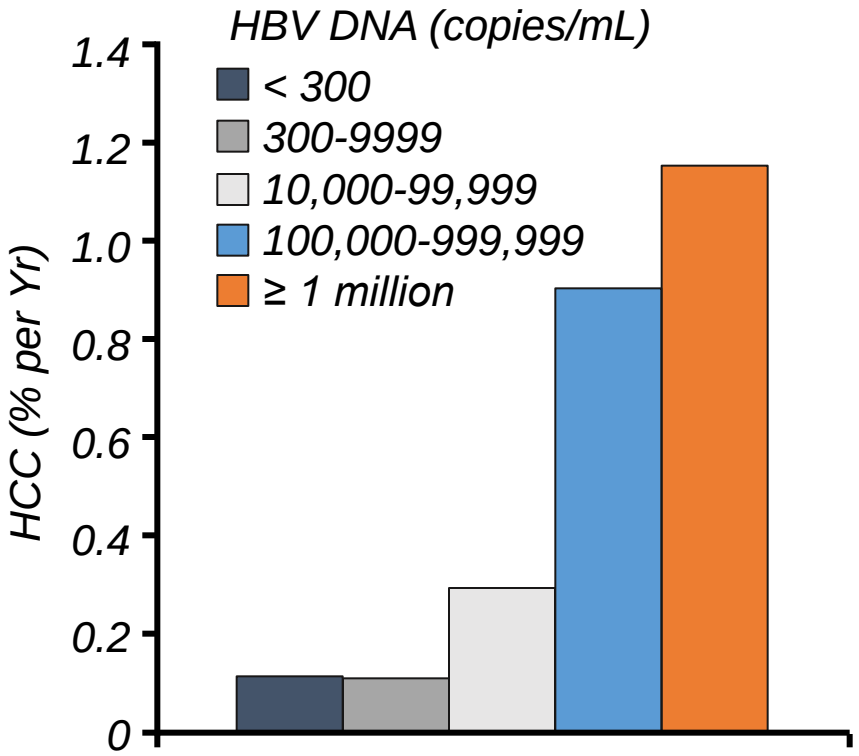
- Main complaint: fatigue
- ALT/AST 1 - 4x upper limit of normal
- Virology HBe(-), HBV-DNA 10e5 copies/ml
- Alfa-fetoprotein: normal

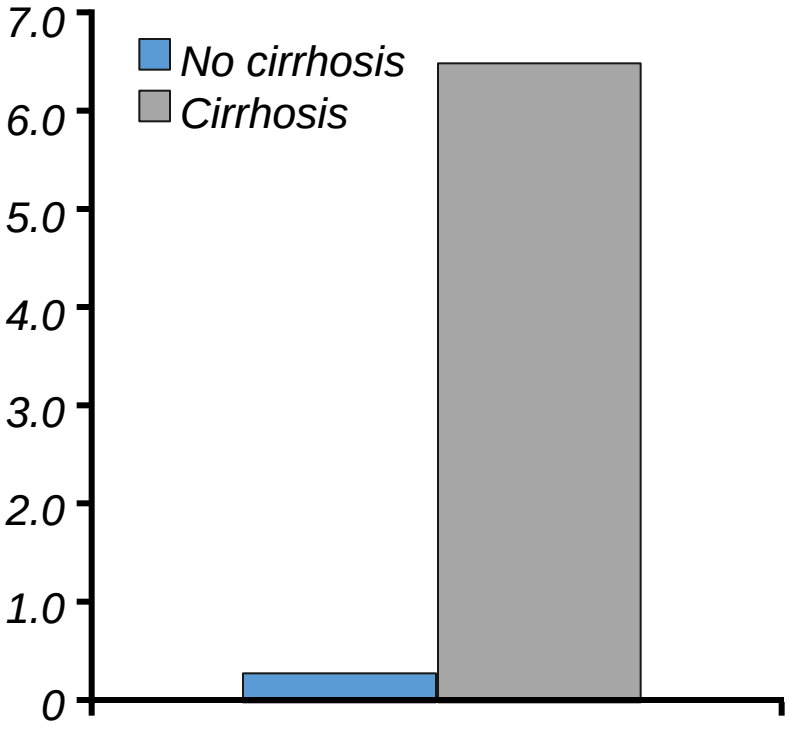
→Adefovir 10 mg was started.

- Imaging: malignant nodule right liver 6 cm
- No signs of cirrhosis or portal hypertension
- Chest X-ray and bone scintigraphy: no abnormalities

Risk of HCC according to Baseline Factors

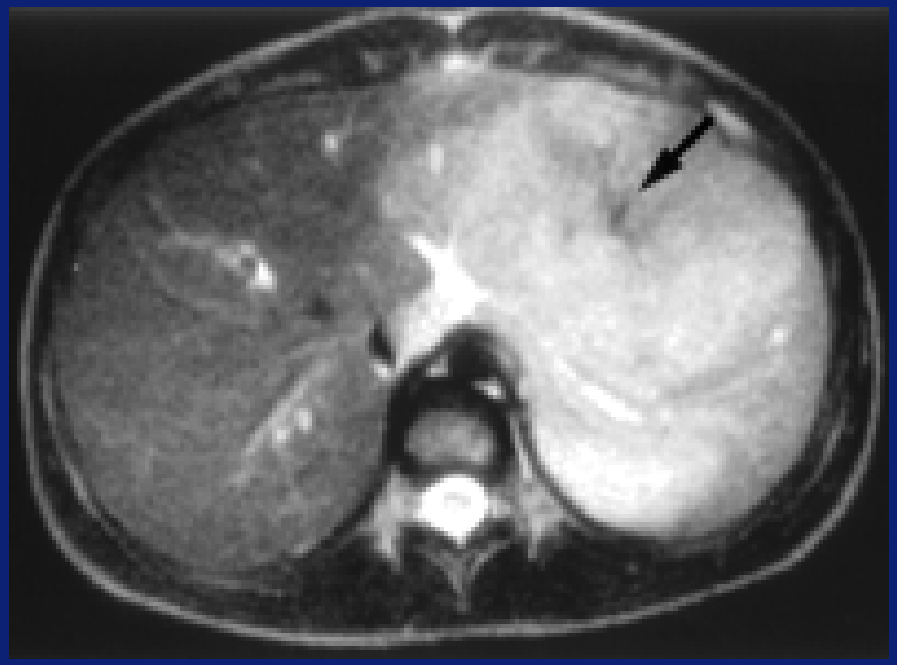
- REVEAL: long-term follow-up (mean: 11.4 yrs) of untreated HBsAg-positive individuals in Taiwan (N = 3653)





Chen CJ, et al. JAMA. 2006;295:65-73

Grootte van de afwijking zegt niets over operabiliteit (in een niet-cirrotische lever)



- Tumor weefsel is niet functioneel leverweefsel
- Functionele overcapaciteit van de lever
- Van belang is de schatting hoeveel parenchym er over blijft (volumetrie) en de kwaliteit van dat parenchym (biopt)

Erasmus MC

The Patient: 2004; what to do ?

1. Refer to the surgeon for resection

2. Liver biopsy form the lesion

3. Local therapy RFA, radiofrequency ablation

4. TACE, chemo embolisation

5. Refer for liver transplantation

Operation 2004

- Hemi hepatectomy right side
- Partial resection diafragm

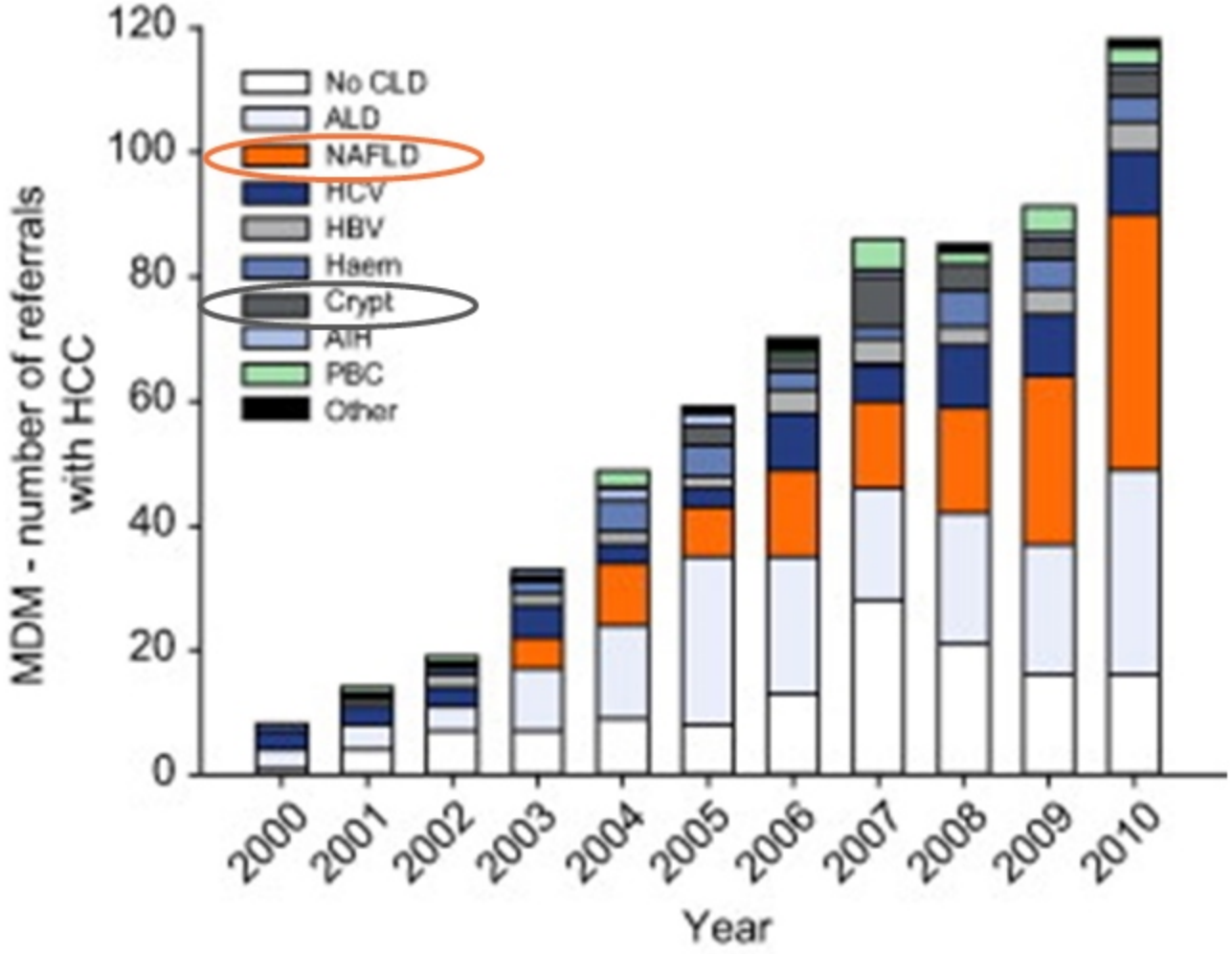
- Pathology:
- HCC, 6 cm, well differentiated, no vasoinvasive growth, free margins.

- Follow-up

Patient 2:

- NASH patient, cirrhosis Child B with portal hypertension
- Imaging: malignant nodule *typical* HCC Right liver *6 cm*
- Chest X-ray and bone scintigraphy: no abnormalities

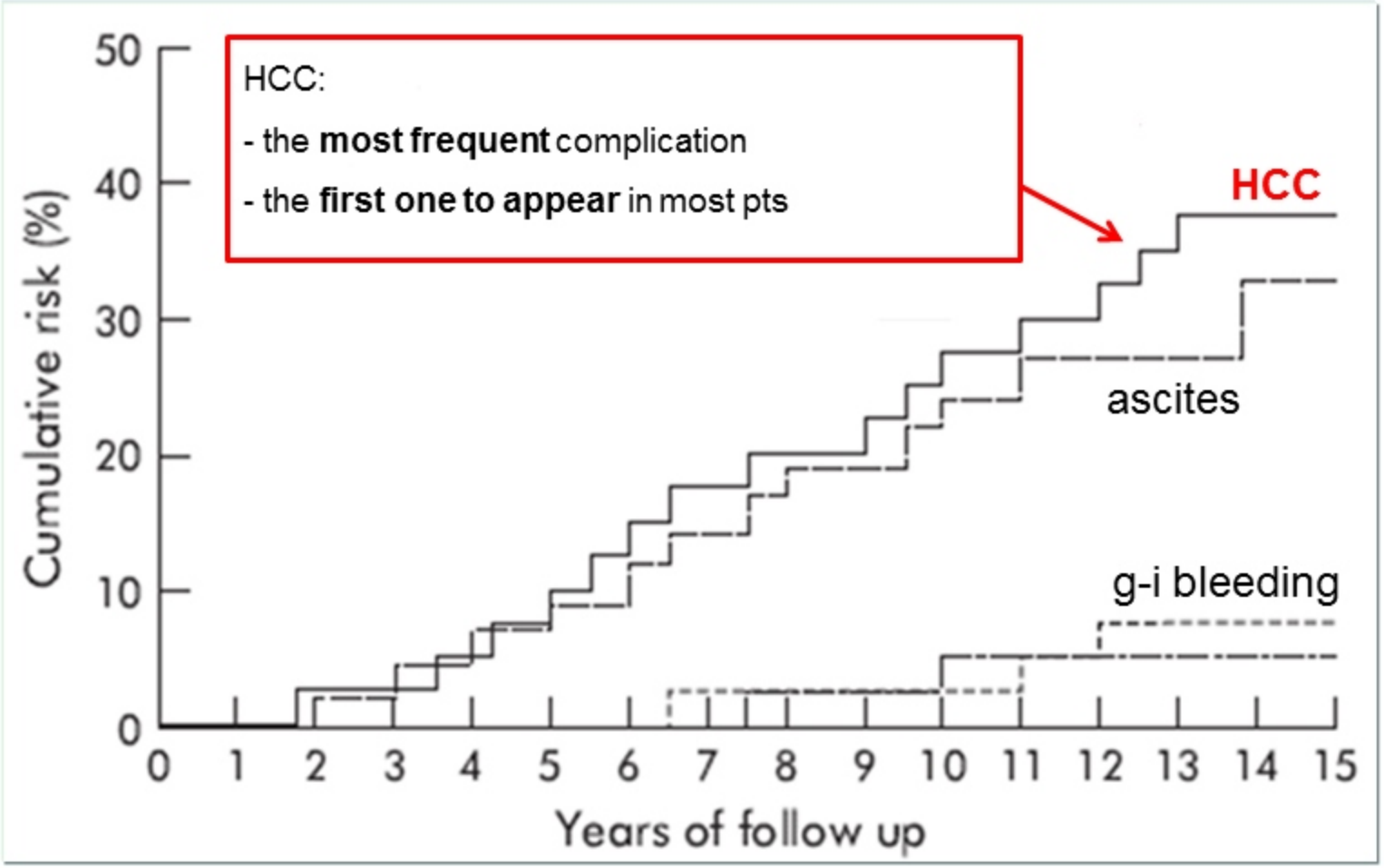
Etiologies of chronic liver disease associated with HCC: an English study



Dyson J et al, J Hepatol 2014; 60:110–117

Temporal trends of complications in initially compensated cirhosis

Child-Pugh class A patients (n = 312), median follow-up: 93 months



Benvegnù L, et al. Gut 2004; 53: 744-9

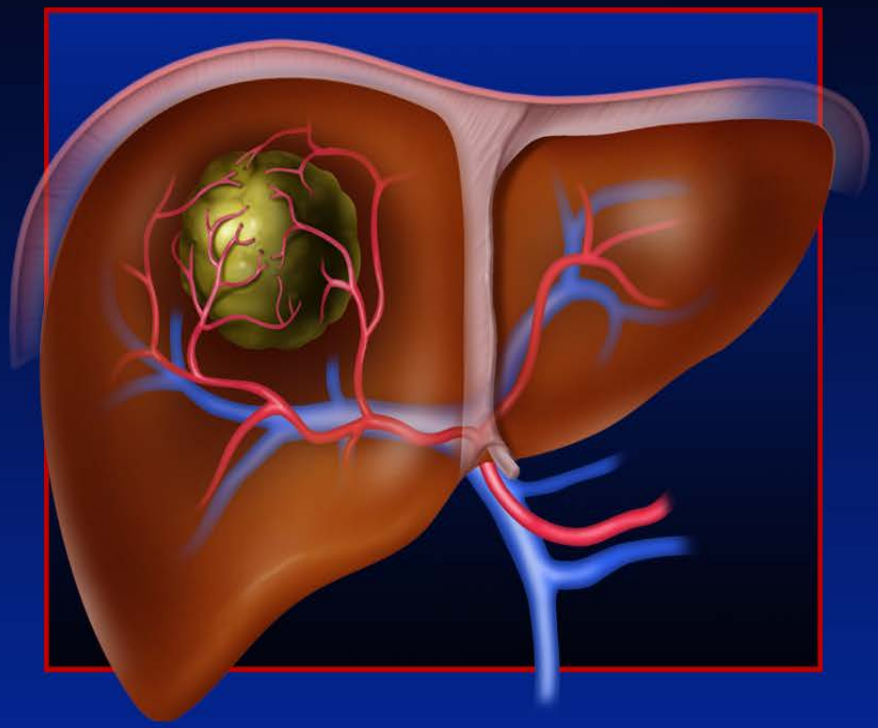
Clinical Features at Presentation

Symptoms	Percent of Patients
None	23%
Abdominal Pain	32%
Ascites	8%
Jaundice	8%
Anorexia/weight loss	10%
Malaise	6%
Bleeding	4%
Encephalopathy	2%

Gastroenterology 2002

Dual Blood Supply of Liver

- The vascular supply of HCC arises from the hepatic artery through neovascularization.
- Imaging of the liver has to be performed in a triple phase manner to account for the early arterial phase followed by the portal venous phase and the delayed phases

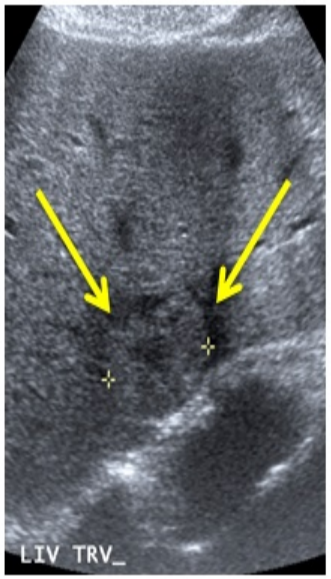


Yu JS, et al, Am J Roentgenol 1999

Classical Scenario

Detection

Ultrasound

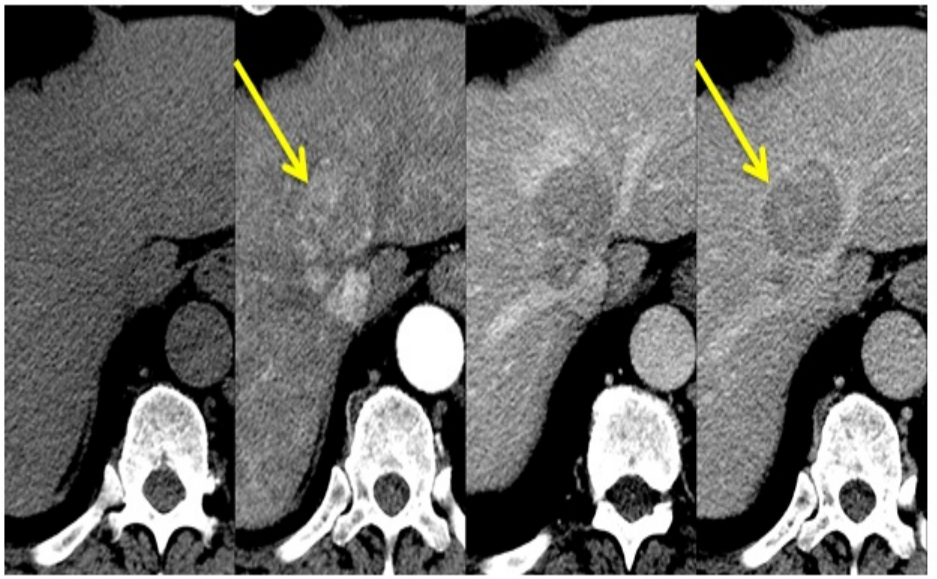


Transverse

"Nodule"

Characterization

Multiphasic CT or MRI

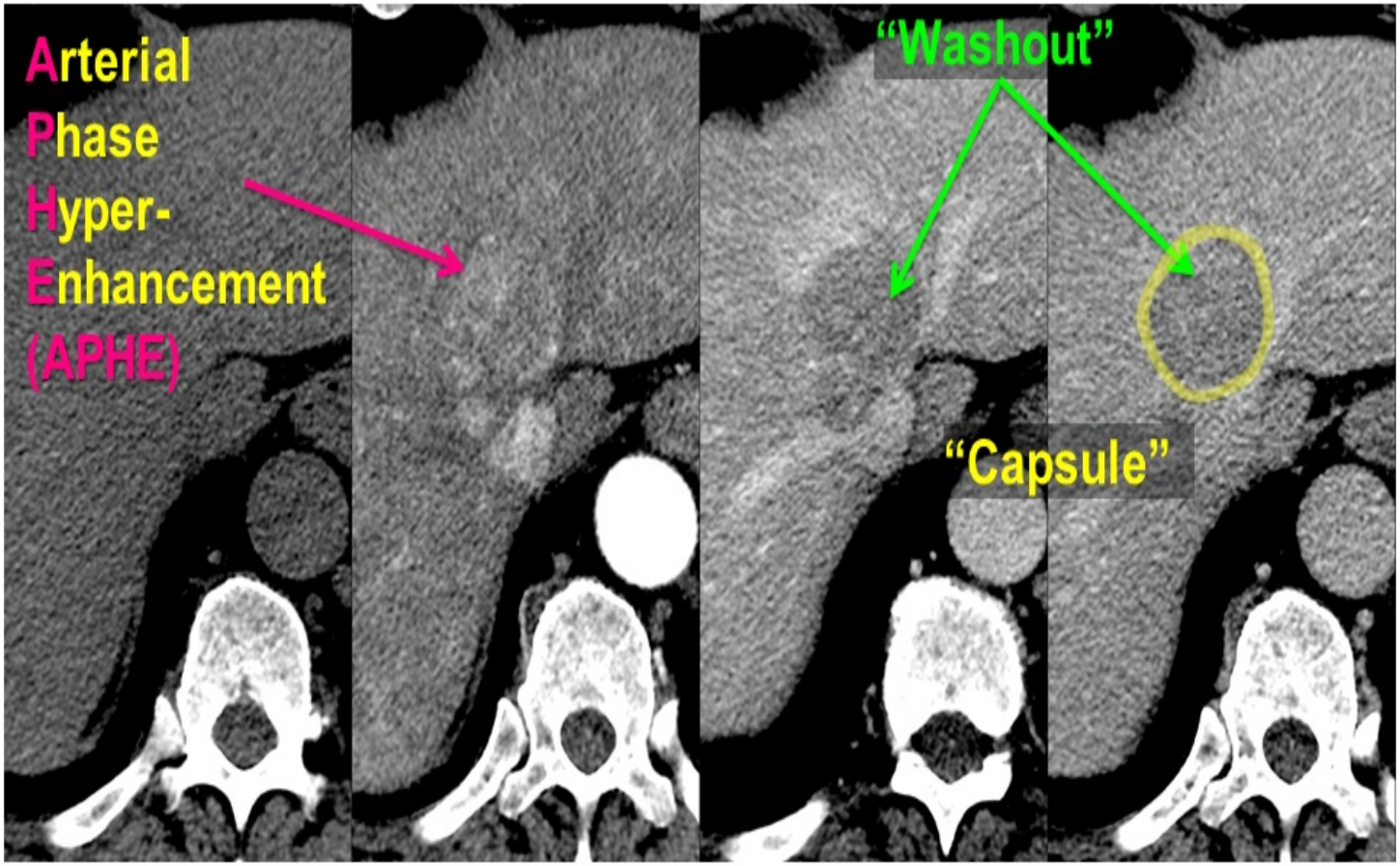


Pre AP PVP 3 min delay

"HCC"

Characterization

Multiphasic CT (or MRI)



Diagnostic Criteria for HCC

EASL
European Association for the Study of the Liver

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

LI-RADS

Imaging criteria
~100% PPV for HCC

Diagnostic Criteria for HCC

Nodule on US

EASL (European Association for the Study of the Liver)

APHE + "Washout"

- CT and MRI-ECA
  - if 10-20 mm
- CT or MRI-ECA
  - if > 20 mm

AASLD (American Association for the Study of Liver Diseases)

APHE + "Washout"

- CT or MRI-ECA
  - if > 10 mm

LI-RADS

APHE + "Washout"

- CT or MRI-ECA or MRI-Gx
  - if ≥ 10 mm

Must be multiphasic

Diagnostic Criteria for HCC

Nodule *not* visible on US, or US not done

EASL European Association for the Study of the Liver	APHE + "Washout"	CT and MRI-ECA • if 10-20 mm CT or MRI-ECA • if > 20 mm
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES	APHE + "Washout"	CT or MRI-ECA • if > 10 mm
LI-RADS	APHE + "Washout"	CT or MRI-ECA or MRI-Gx • If ≥ 10 mm

Diagnostic Criteria for HCC

Nodule ***not*** visible on US, or US not done

- If 10-19 mm: APHE + 2 or more other major features
- If ≥ 20 mm: APHE + 1 or more other major features

Multiphasic CT or MRI-ECA or MRI-Gx

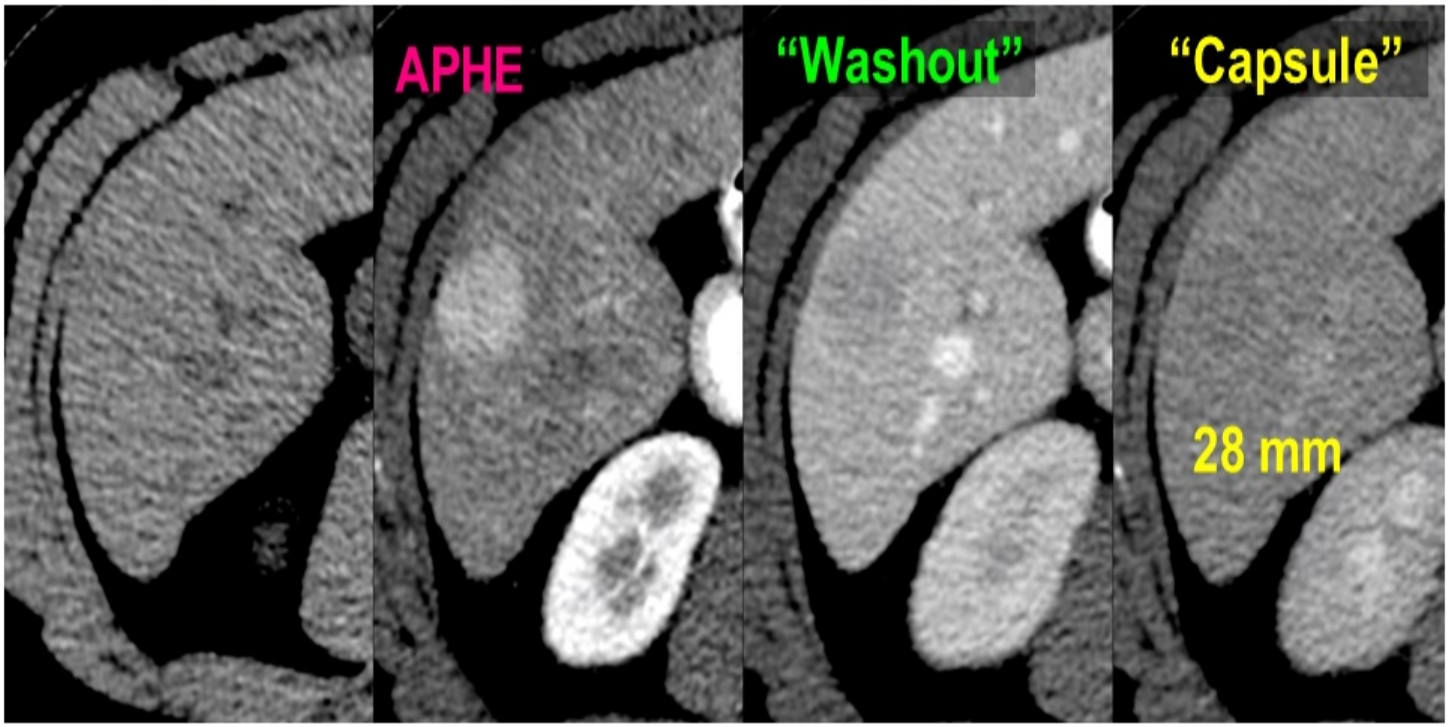
LI-RADS

Other major features =

- "washout", "capsule", growth

Diagnostic Criteria for HCC

54-year-old woman, no liver disease



Don't: apply imaging criteria to general population!

Do: apply criteria to patients at risk for HCC!

Don't Meet Diagnostic Criteria for HCC

EASL
European Association for the Study of the Liver

→ Biopsy

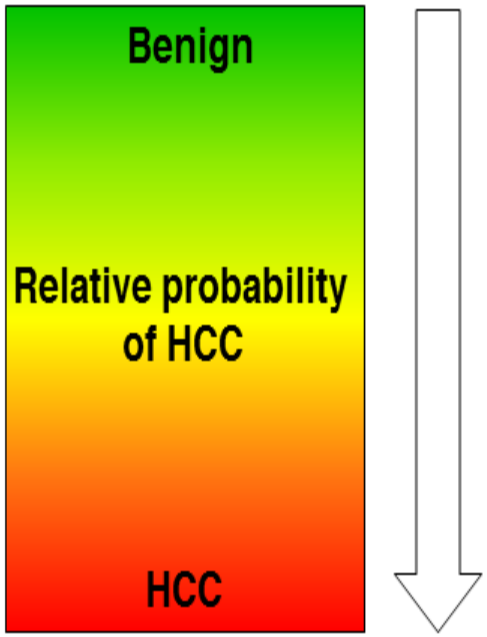
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

→ Biopsy

LI-RADS

→ Individualized management

Don't Meet Diagnostic Criteria for HCC



LI-RADS Categories

LI-RADS → **Individualized management**

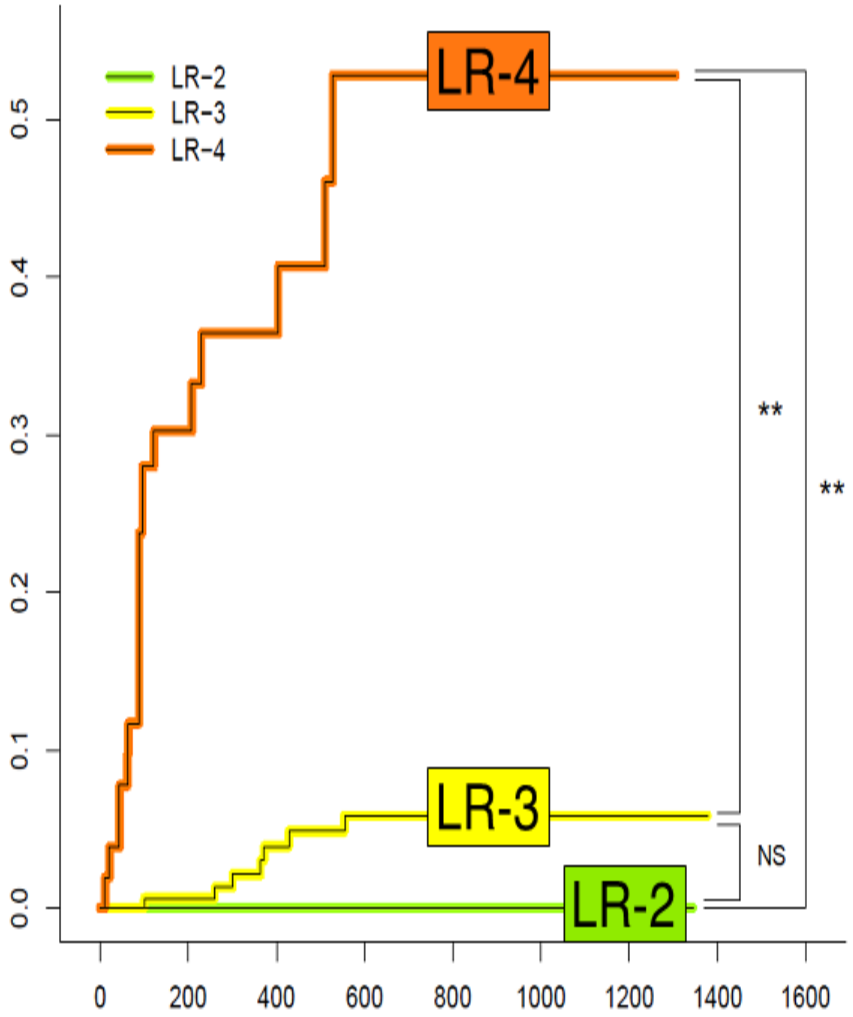
Don't Meet Diagnostic Criteria for HCC

LR-1	Definitely benign
LR-2	Probably benign
LR-3	Intermediate probability for HCC
LR-4	Probably HCC
LR-5	Definitely HCC
LR-M	Probably malignant, not necessarily HCC

Individualized management

LR-2 LR-3 LR-4

Cumulative incidence of progression to malignancy



Days until progression

Take Home Messages

EASL, AASLD, LI-RADS: imaging criteria for HCC

- ~100% positive predictive value for HCC
- Apply ***only*** to high-risk patients

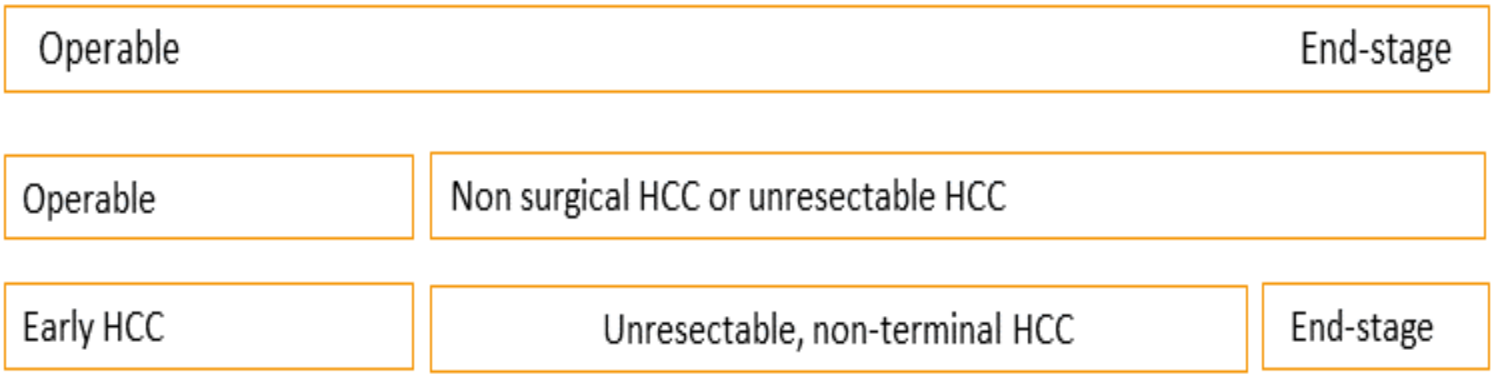
Algorithms non-identical

- EASL and AASLD
  - US detected nodules; CT or MRI-ECA
- LI-RADS
  - Any nodules; CT or MRI-ECA or MRI-Gx

Nodules that don't meet HCC criteria

- EASL and AASLD → biopsy
- LI-RADS → individualized management, informed ***in part*** by LR category

The BCLC concept development



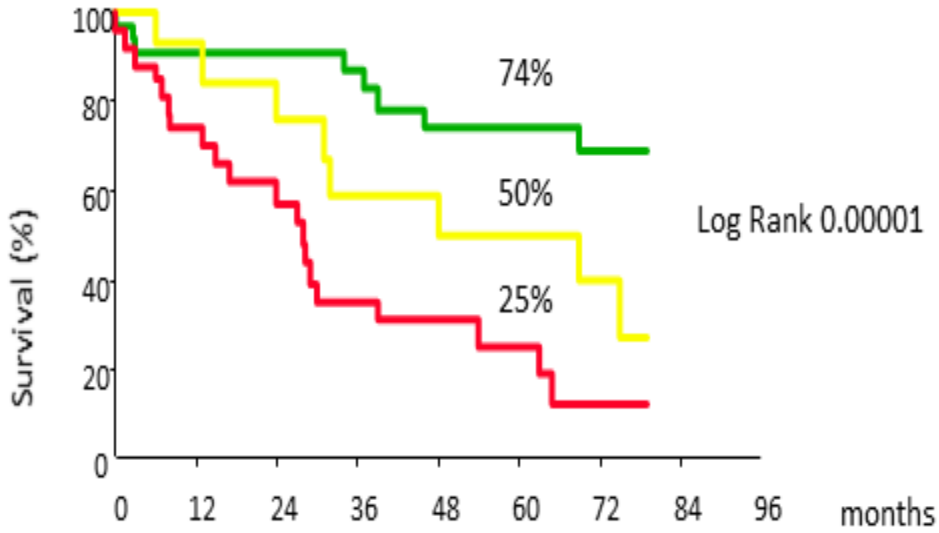
Curative treatments: Surgical Resection

Prognosis of HCC suitable to resection

Best candidates: - Solitary HCC

- Child-Pugh A: No portal hypertension (HVPG < 10 mmHg)

Normal Bilirubin (< 1 mg/dl)

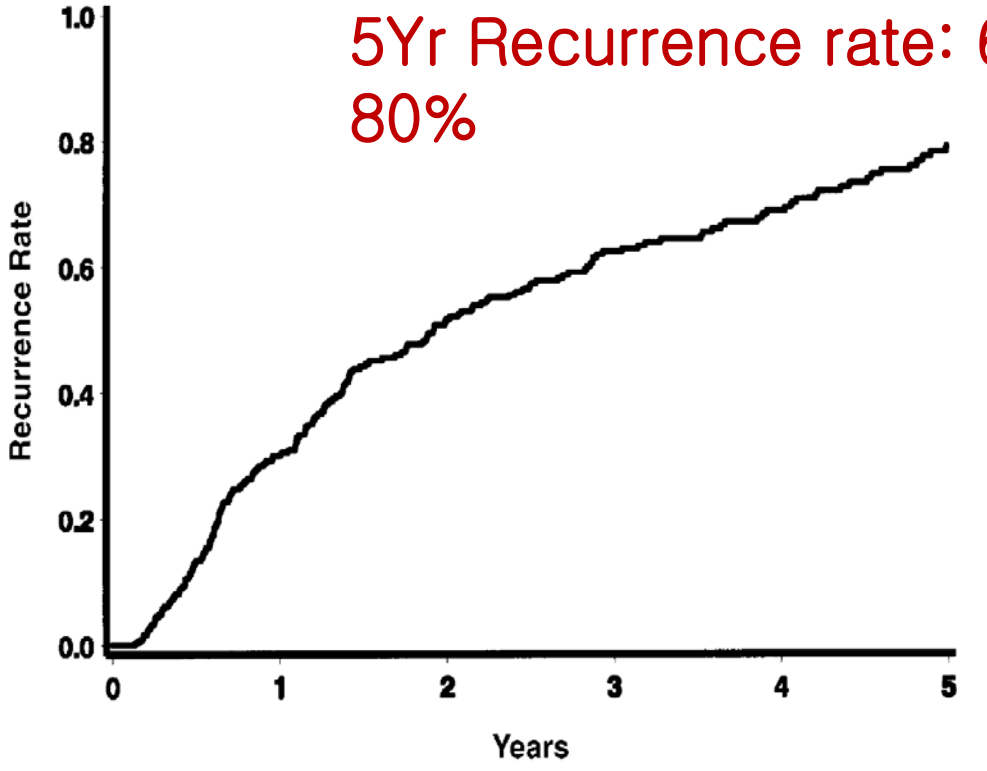


Llovet JM, et al. Hepatology. 1999;30:1434-40.

HCC Recurrence rate after resection

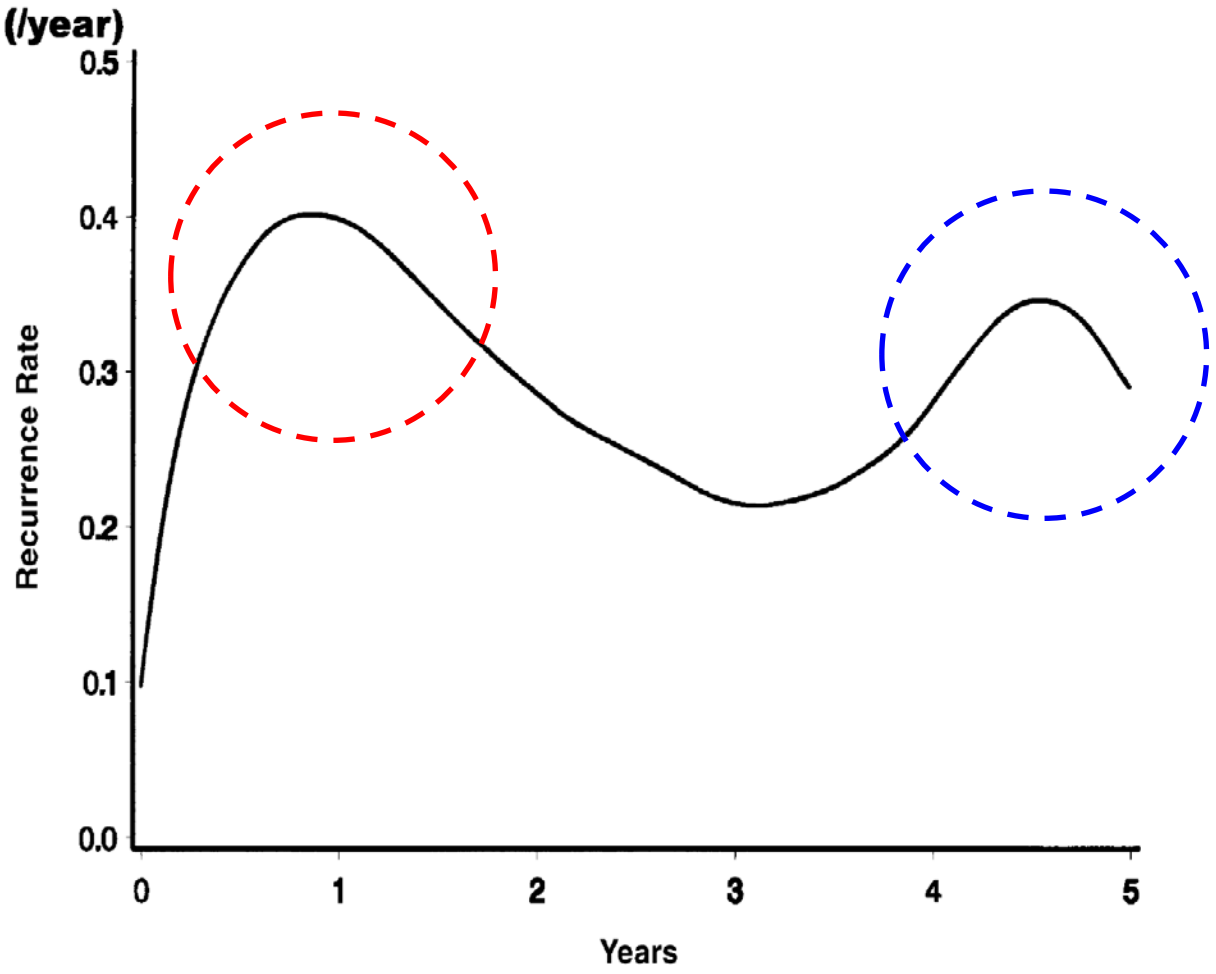
5Yr Survival rate: 50–70%

5Yr Recurrence rate: 60–80%



H. Imamura et al. Journal of Hepatology 2003:38:200-207

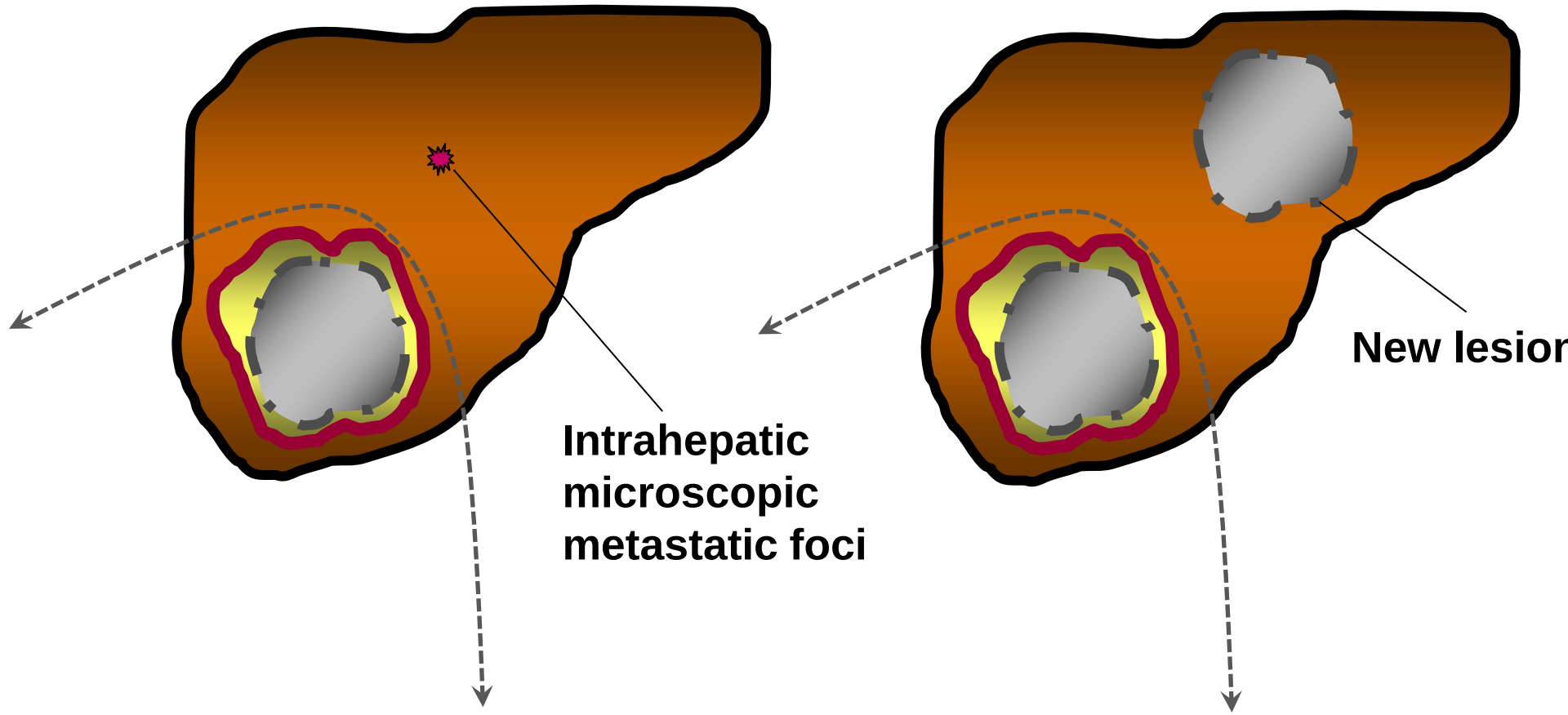
Bimodal recurrence after HCC resection



H. Imamura et al. Journal of Hepatology 2003:38:200-207

Early recurrence;
intrahepatic metastasis

Late recurrence;
de novo carcinogenesis



Curative treatments: Liver transplantation

Outcomes applying restrictive selection criteria

Authors, year	n	Selection criteria	Recurrence	Survival at 5y
Mazzaferro, 1996	48	Milan	8%	74%*
Jonas, 2001	120	Milan	15%	71%
Cillo, 2004	30	Milan	6.7%	72%
Herrero, 2008	47	Milan	8.5%	70%
Mazzaferro, 2009	444	Milan	5.5%	73.3%

* Survival at 4 years
~ 5-y recurrence rate
¬ 100-(5-y RFS)

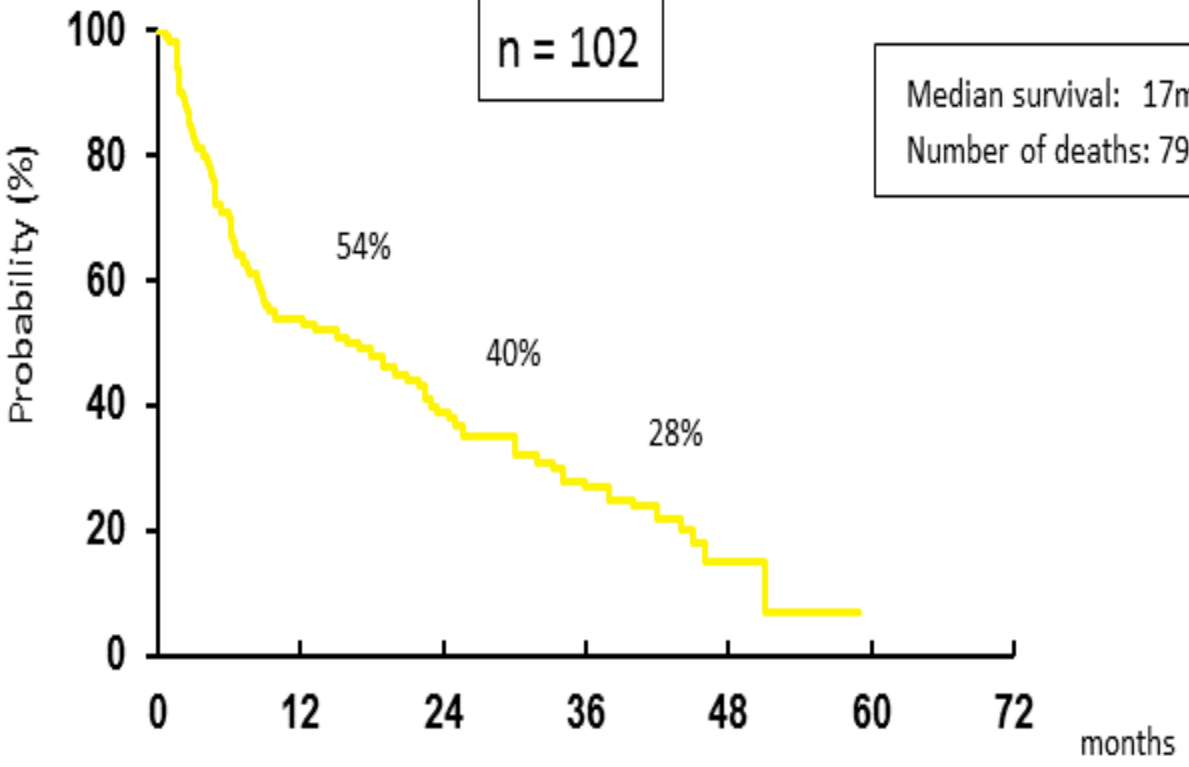
Mazzaferro V et al. N Engl J Med. 1996;334:693-9
Jonas S et al. Hepatology. 2001;33:1080-6
Cillo U et al. Ann Surg. 2004;239:150-9
Herrero JI et al. Liver Transpl. 2008;14:272-8
Mazzaferro V et al. Lancet Oncol. 2009;10:35-43
Kulik LM et al. Am J Transplant. 2012;12(11):2997-3007

Natural history of non-surgical HCC

Tamoxifen (n= 58) vs control (n=62)
Castells A. Gastroenterology, 1995

TAE (n= 40) vs control (n=40)
Bruix J. Hepatology, 1998

n = 102



Median survival: 17m
Number of deaths: 79 pts

Patients at risk	102	57	40	21	8	1

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

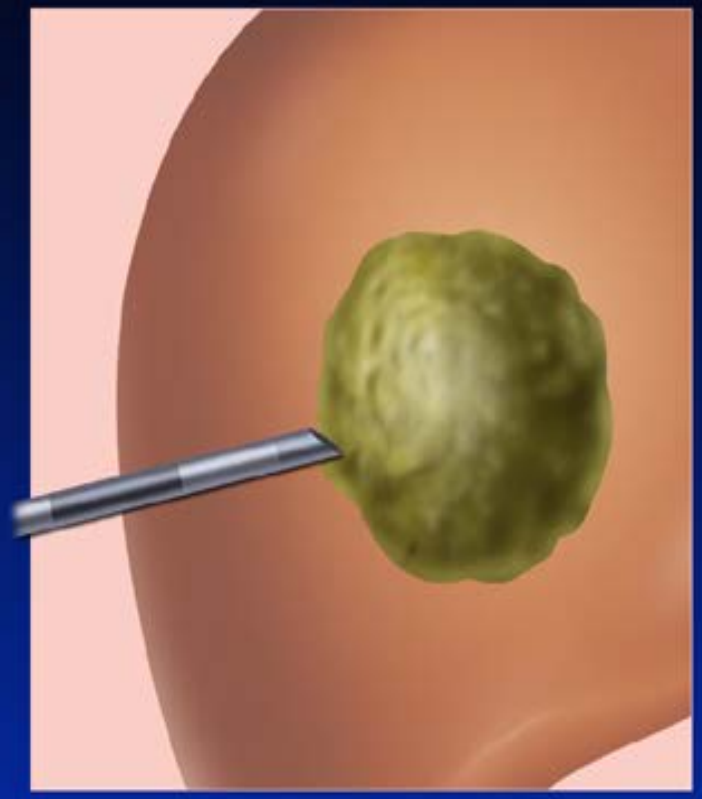
Natural history of non-surgical HCC

Prognostic factors in the multivariate analysis

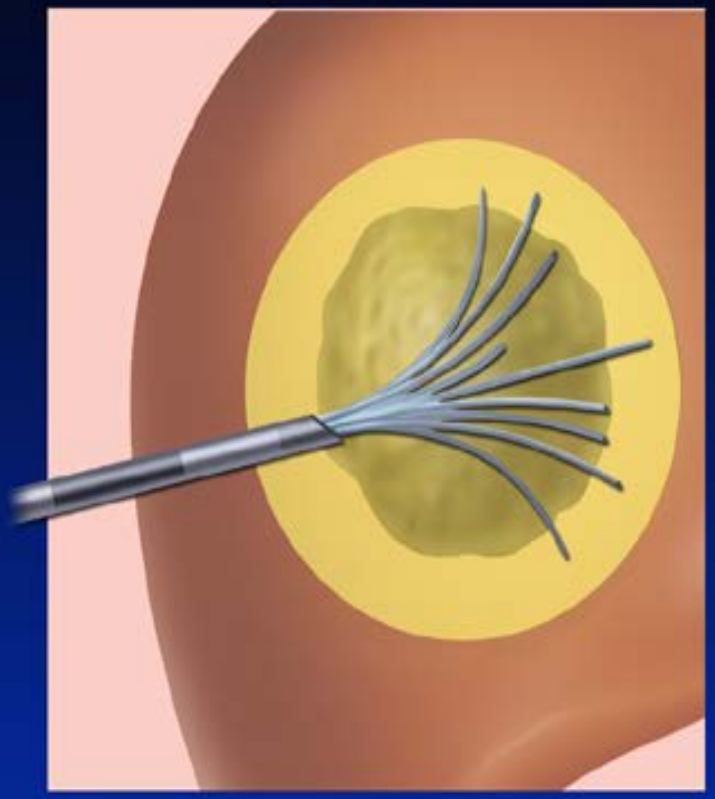
Variables		OR (95% CI)	p value
Performance status	1	1.2 (0.7-1.9)	0.0171
	2	1.5 (0.8-2.9)	
Constitutional syndrome		1.4 (1.1-1.9)	0.046
Portal thrombosis		1.9 (1.2-2.9)	0.0013
Extrahepatic spread		1.67 (1.1-2.7)	0.048

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

Radiofrequency Ablation for Hepatocellular Carcinoma

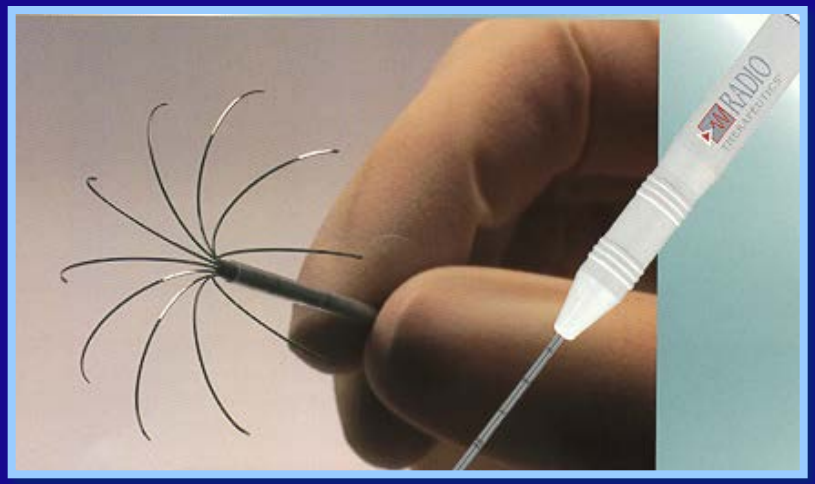


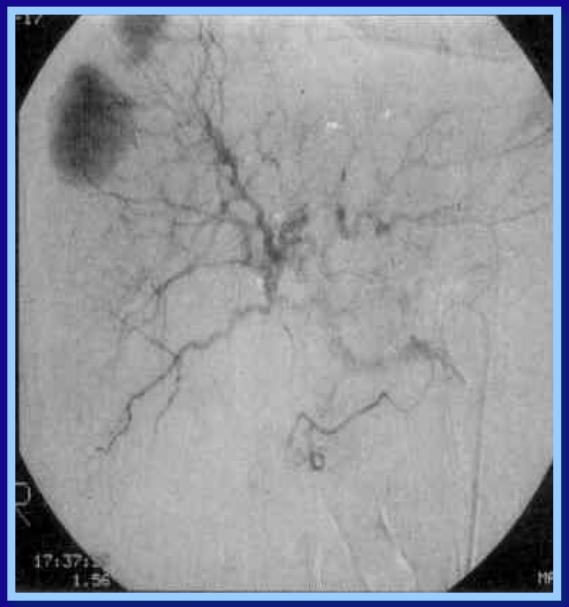
Probe insertion

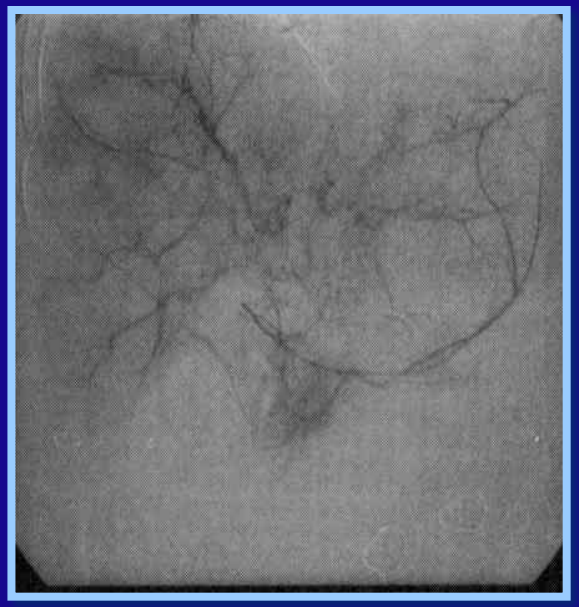


Deployment of tines and treatment of tumor and surrounding region

Radiofrequency Ablation

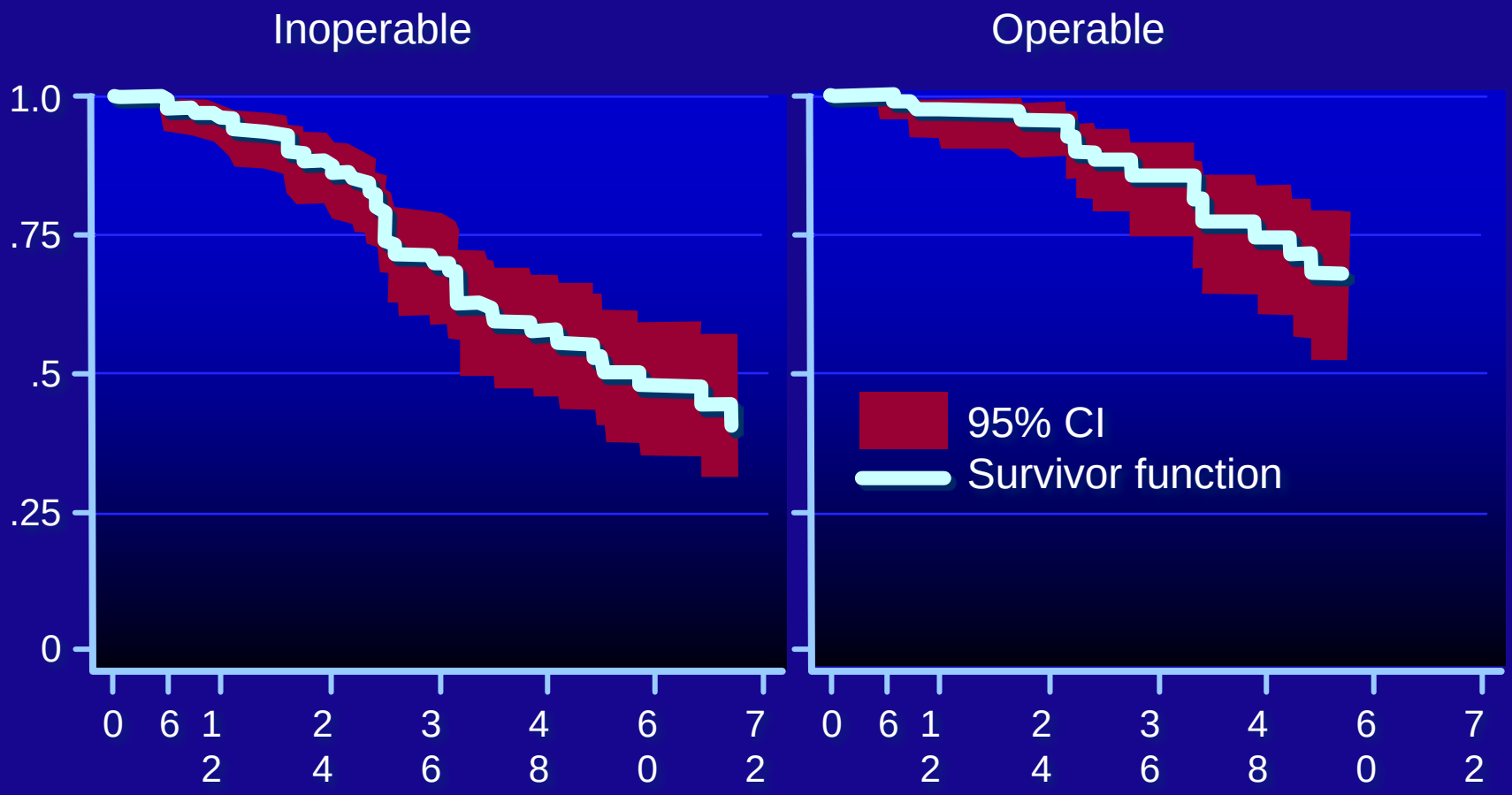






Prospective Study of RFA in Early HCC

Kaplan-Meier survival estimates, by operability



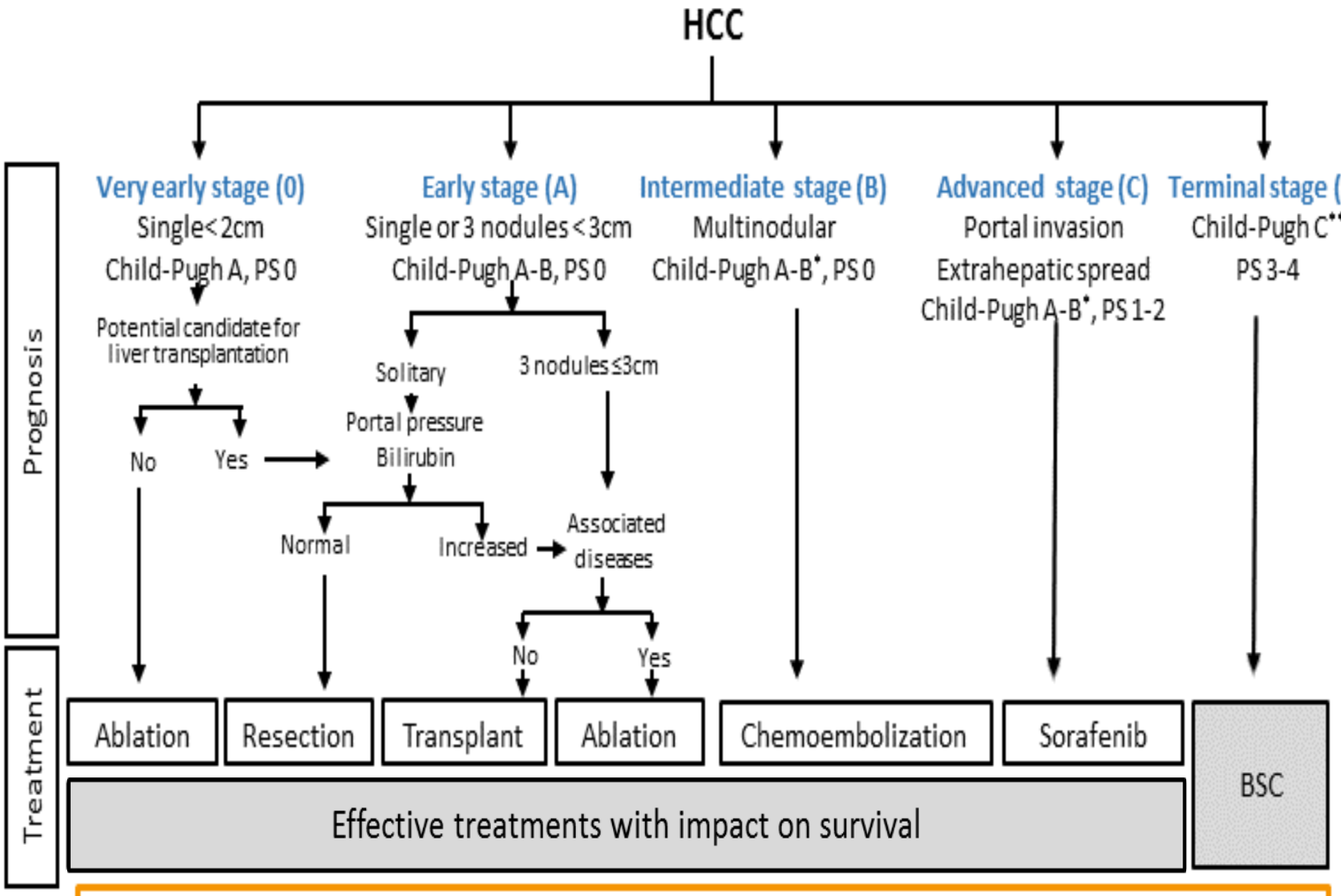
97% complete response upon a median F/U time of 31 mo

Livraghi T, et al. Hepatology. 2008; 47:429

Staging Systems for Hepatocellular Carcinoma

- Okuda Staging System
- Cancer of the Liver Italian Program (CLIP)
- American Joint Commission on Cancer (AJCC)/Union Internacional Contra la Cancrum (UICC) Tumor Node Metastasis (TNM)
- Japanese Staging System and Japan Integrated Staging score (JIS)
- Chinese University Prognostic Index (CUPI)
- Barcelona Clinic Liver Cancer (BCLC)
- Group d'Etude de Traitement du Carcinoma Hepatocellulaire (GRETCH)

BCLC Staging and Treatment Strategy, 2016

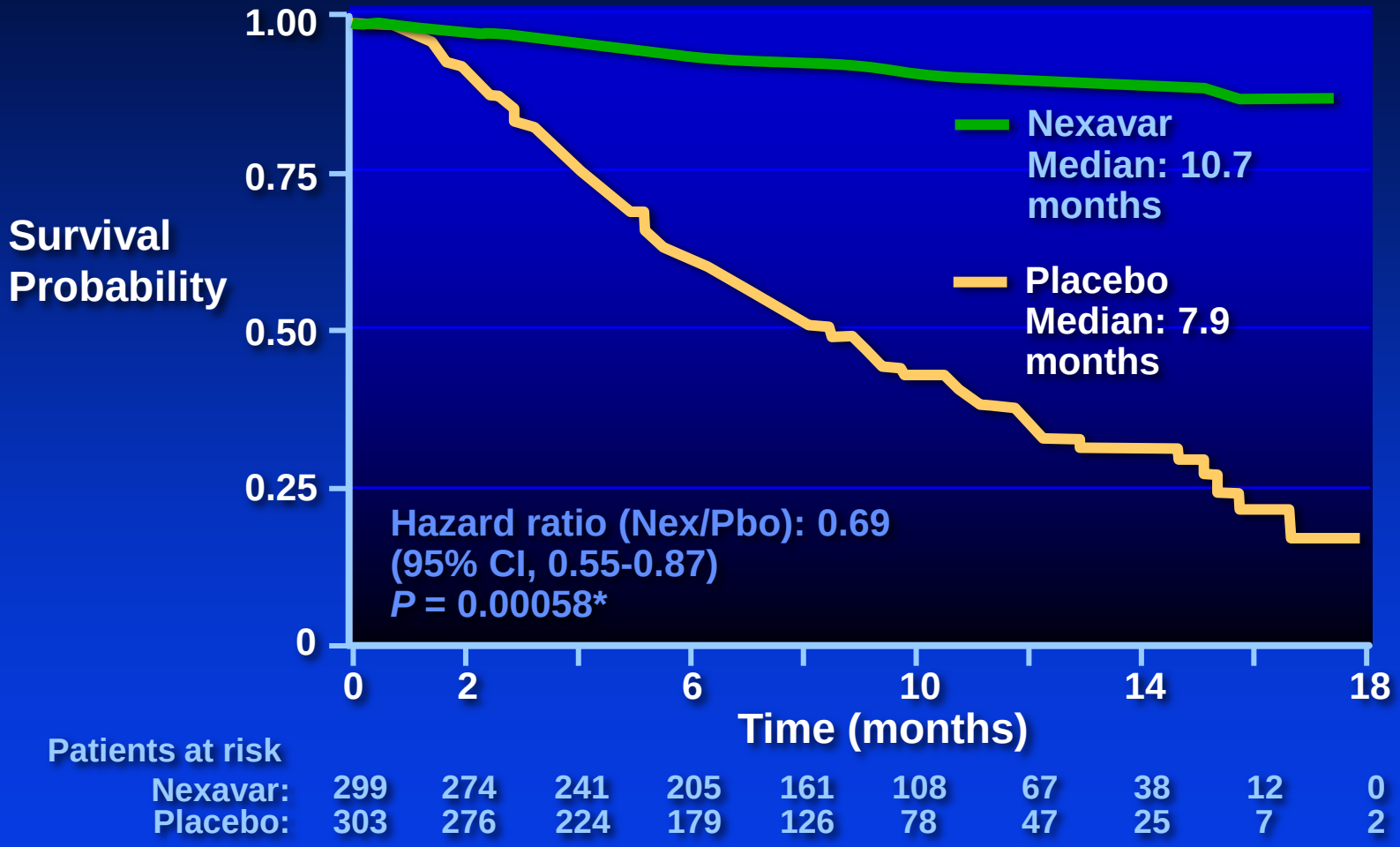


* Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.

** Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In the, HCC may become a contraindication if exceeding the enlistment criteria.

Bruix J, Reig ME, Sherman M. Gastroenterology 2016: Apr;150(4):835-53.

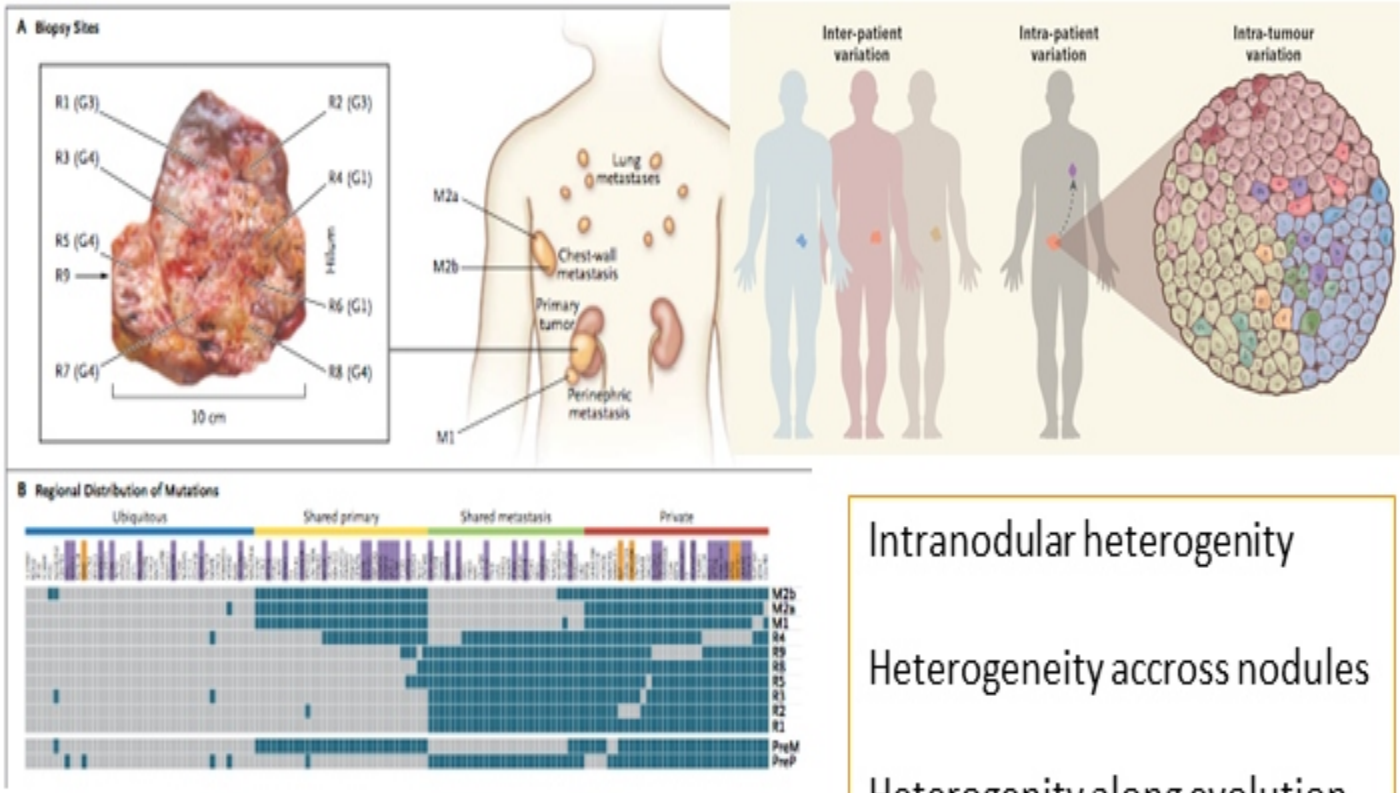
Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)



Llovet JM et al. *NEJM.* 2008; 359(4):378

Molecular classification of HCC

Limited by intratumor Heterogeneity



Intranodular heterogenity

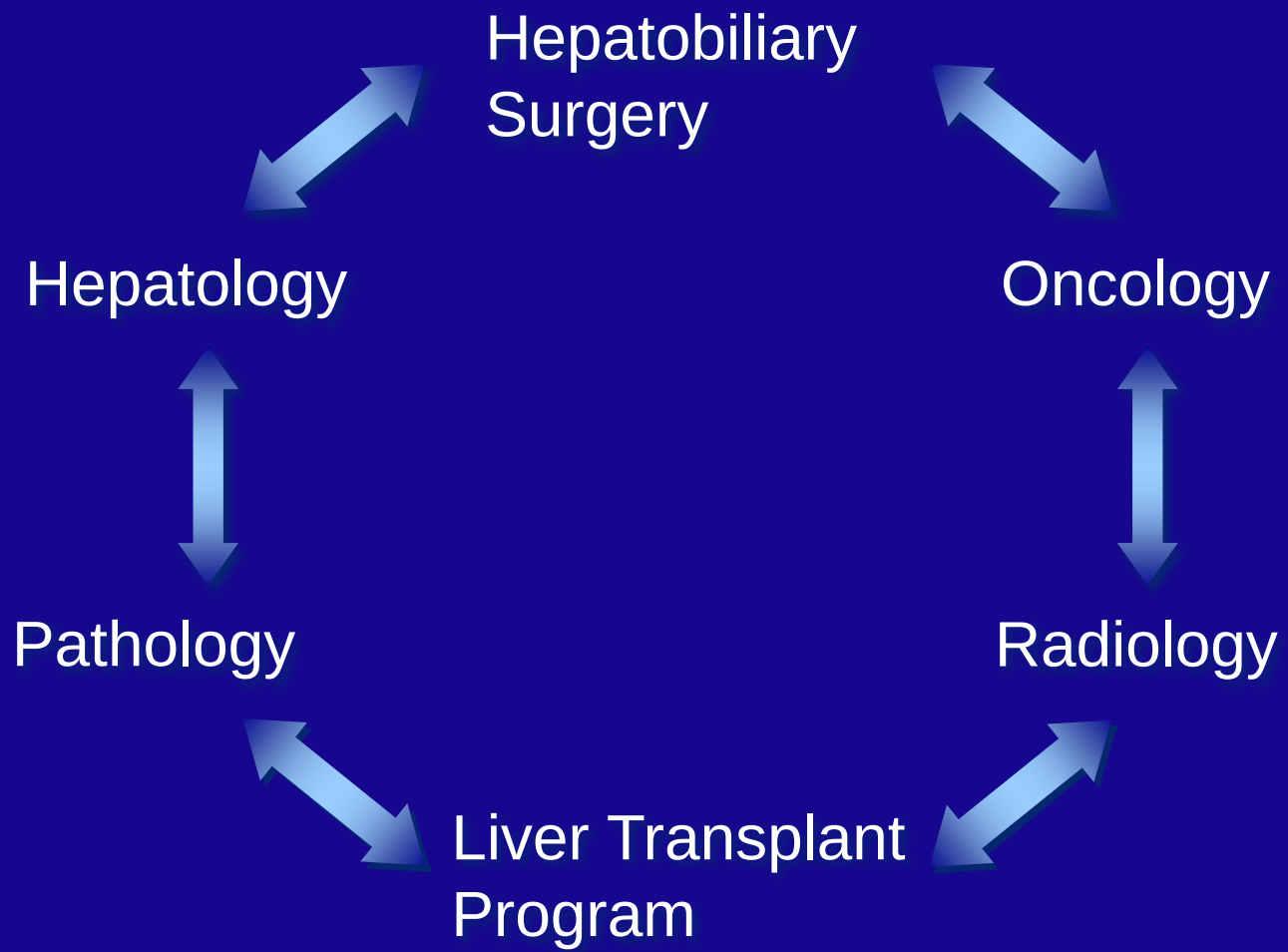
Heterogeneity accross nodules

Heterogenity along evolution

Gerlinger M et al. N Engl J Med. 2012:366:883-92.

Fox EJ, and Loeb LA. Nature 2014;14;512(7513):143-4.

Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach



Teaching Aims

- Understand the difference between the diagnostic work-up of a nodule in liver cirrhosis and non-cirrhotic liver disease.
- Therapy selection in HCC depends on
  - extent of liver disease
  - extent of tumor burden
  - performance status of the patient
  - patient preference
  - (available treatment modalities in center)
- Systematic approach using guidelines:
  - IKNL www.oncoline, AASLD, EASL, Lirads, BCLC

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