AIRTUM - XIV Corso di aggiornamento per operatori dei registri tumori

Diagnosi e terapia dei tumori del fegato

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UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

Outline

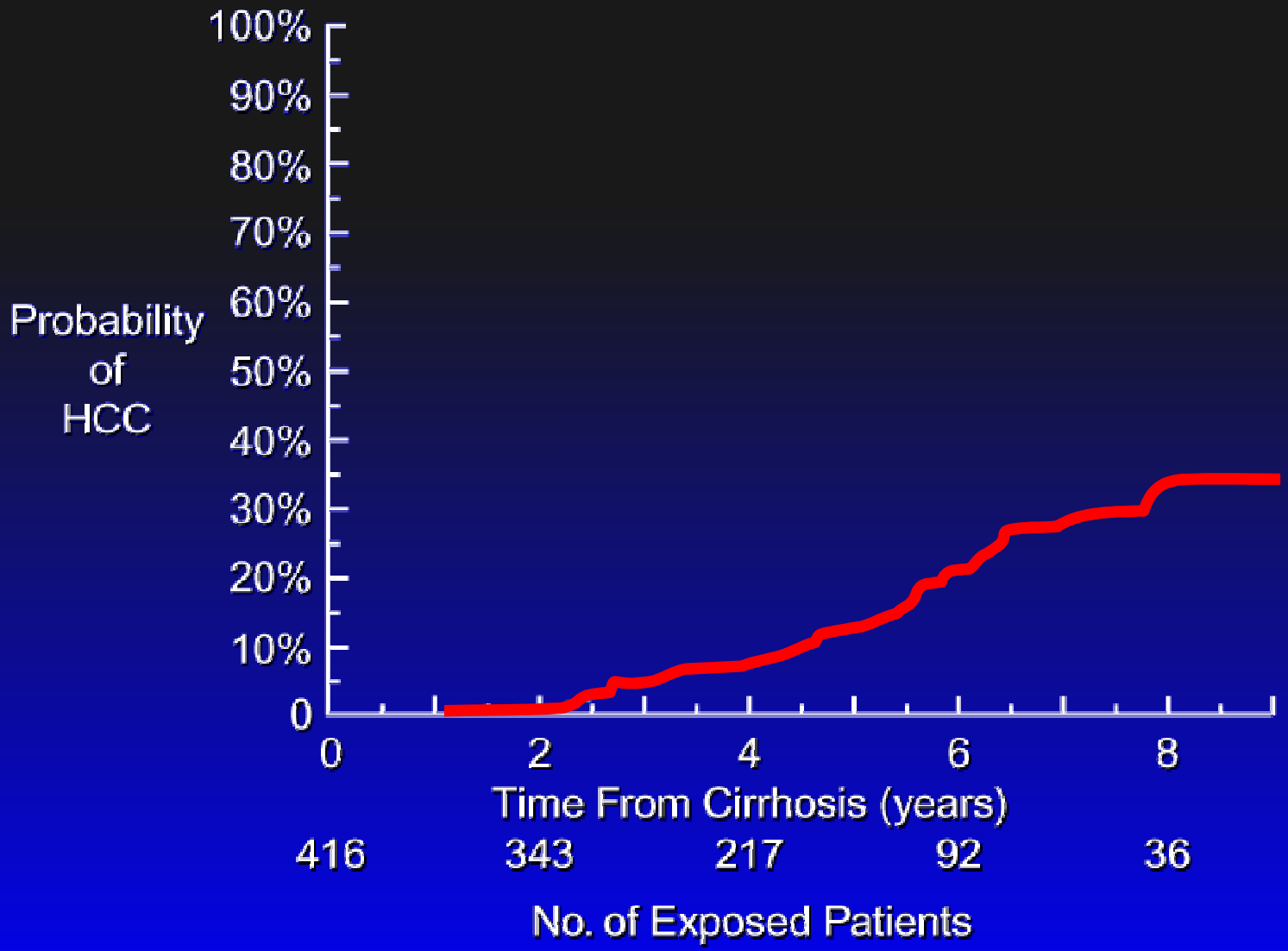
- Definition
- Epidemiology
- Biology
- Diagnosis
- Current Therapies
- Future of Targeted Therapy

What really is HCC?

HCC is the expected complication of long-standing chronic liver disease.

If patients survive the other expected complications (bleeding, liver failure, sepsis), they will invariably develop HCC.

Progression to HCC From Cirrhosis



Degos F et al. *Gut.* 2000;47:131-136.

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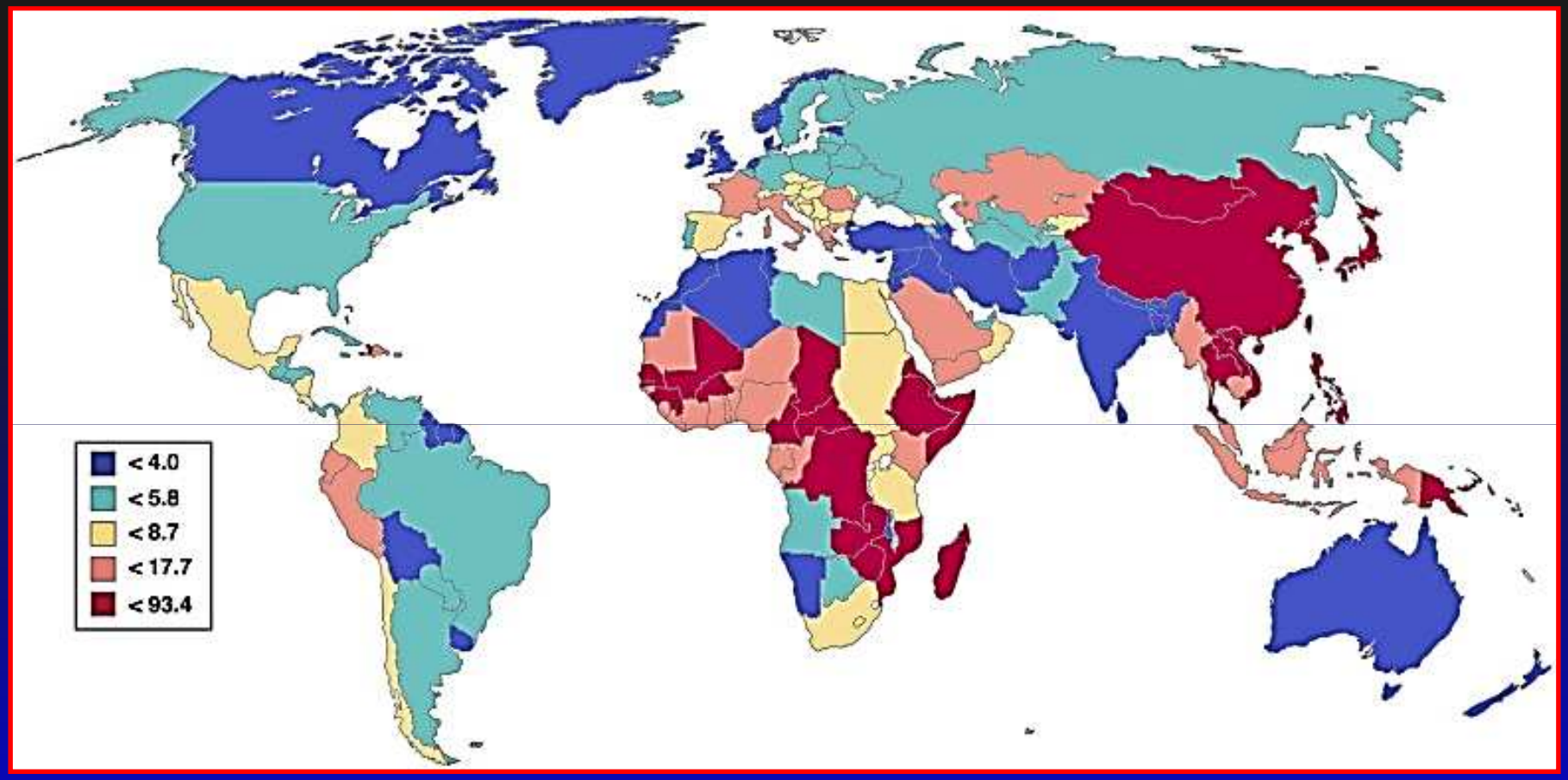
HCC Risk Factors

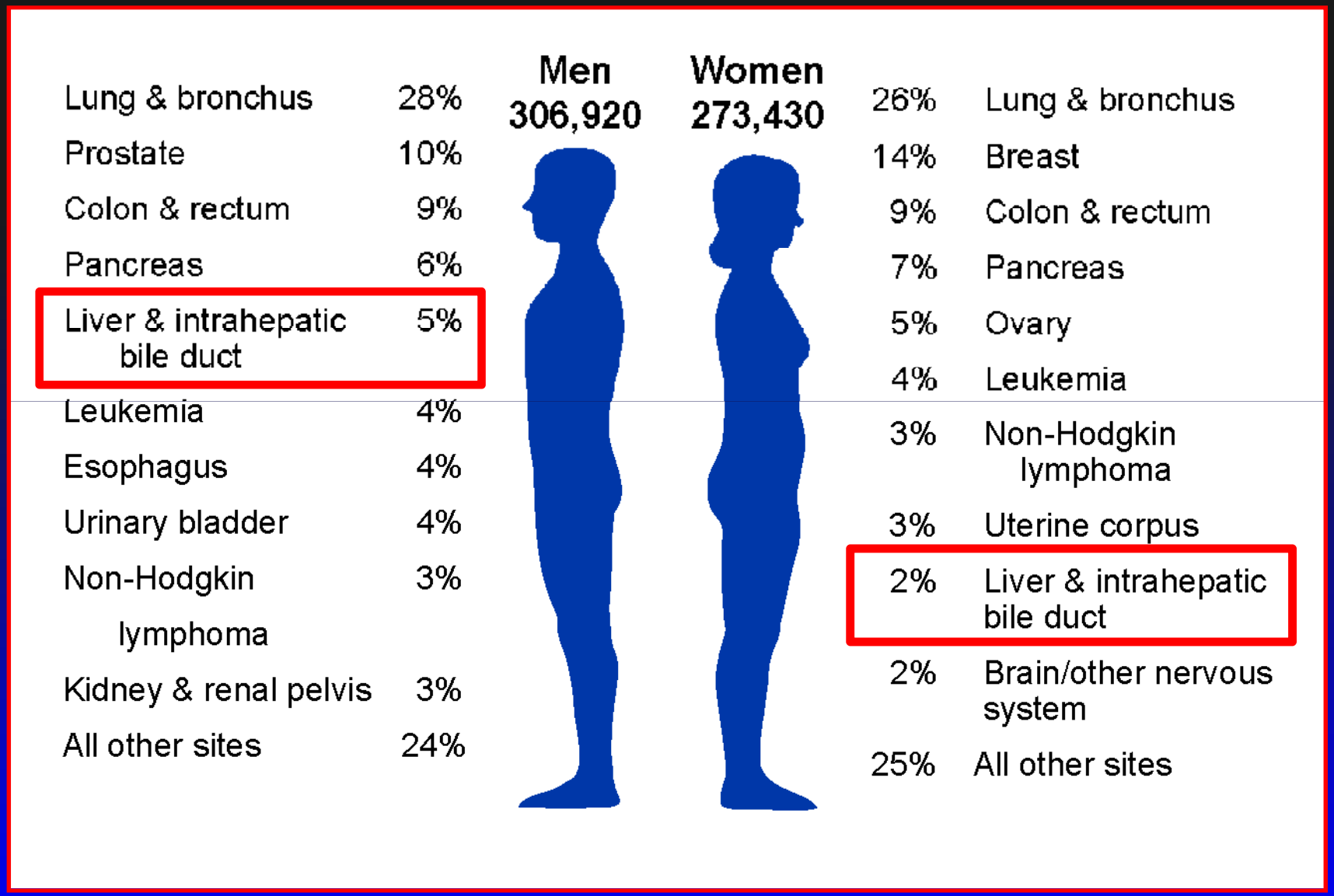
- Exposures
  - HCV, ETOH, Aflatoxin
  - HBV
    - HBV viral load>10^4 copies/ml, genotype C, e antigen positive
- Genetic susceptibility
  - hereditary hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease
- Metabolic factors
  - NASH, metabolic syndrome
  - Demographics
    - Older age, male sex

Liver Cancer Mortality Worldwide

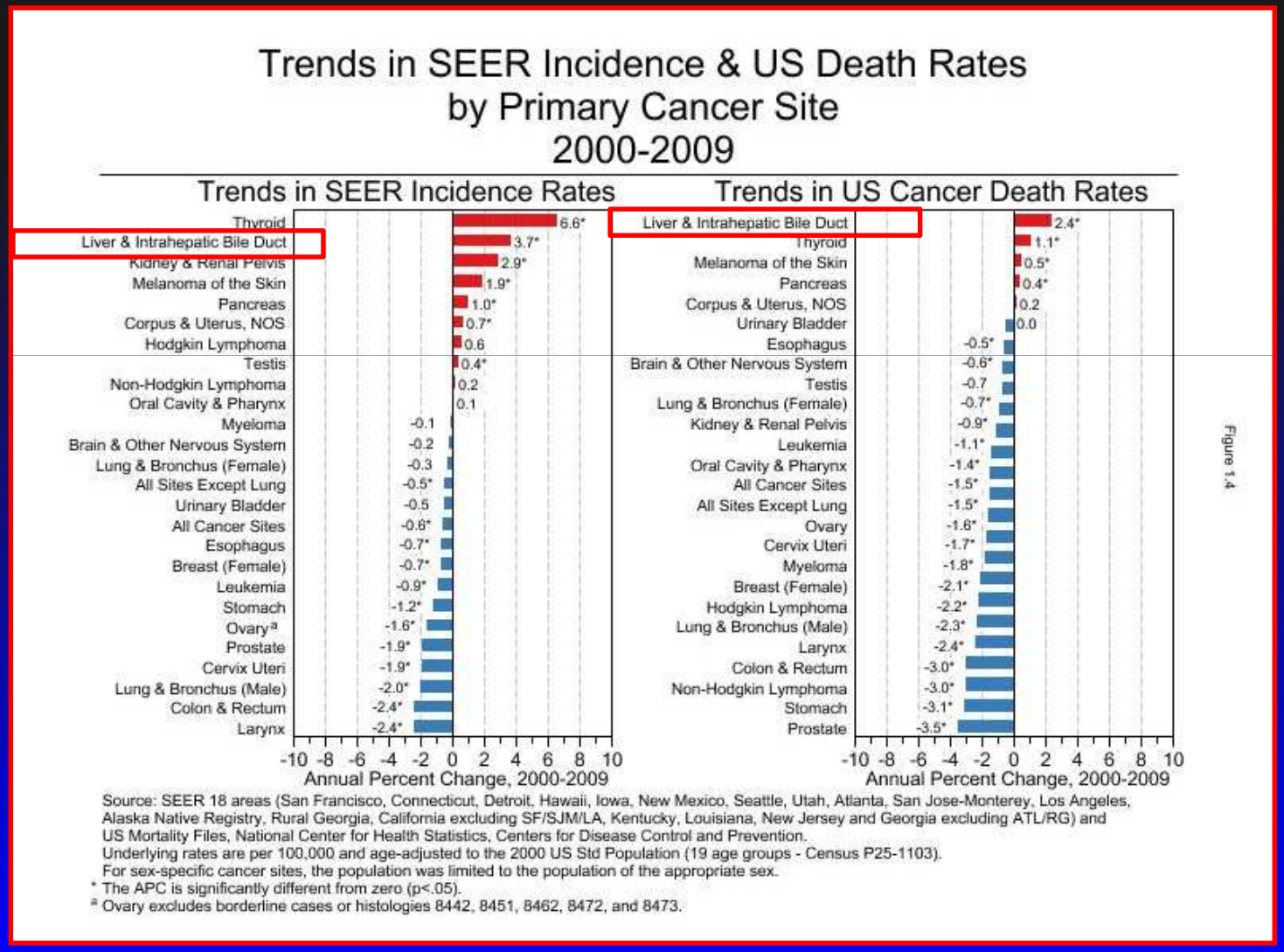


El-Serag and Rudolph, Gastroenterology, 2007

Estimated Cancer Incidence in US in 2013



HCC Incidence and Death Rates are Increasing in the US



Application of the ADRESS-HCC Risk Model to Hypothetical Patients With Cirrhosis

Patient	*A*ge	*D*iabetes	*R*ace	*E*tiology	*S*ex	*S*everity	ADRESS-HCC Score	1-Year HCC Risk, %
1[a]	1.957	0	0	0	0	0.5850	2.542	0.2
2[b]	1.957	0	0.2058	1.246	0	0.8190	4.228	1.0
3[c]	3.029	0	0	0.3509	0.5114	0.9360	4.827	1.7
4[d]	2.330	0.2135	0.2058	1.246	0.5114	1.287	5.794	4.6

Abbreviations: ADRESS, *a*ge, *d*iabetes, *r*ace, *e*tiology of cirrhosis, *s*ex, and *s*everity; HCC, hepatocellular carcinoma.

[a] Patient 1 is a 42-year-old white woman with autoimmune hepatitis, no diabetes, and a Child-Turcotte-Pugh (CTP) of score of 5.

[b] Patient 2 is a 42-year-old Asian woman with hepatitis C, no diabetes, and a CTP score of 7.

[c] Patient 3 is a 65-year-old white man with alcohol-related cirrhosis, no diabetes, and a CTP score of 8.

[d] Patient 4 is a 50-year-old Asian man with hepatitis B cirrhosis, diabetes, and a CTP score of 11.

Flemming et al., Cancer 2014

Association Between Sex and OS on Multivariate Analysis

	Adjusted Median OS (95% CI), Months		HR (95% CI)[a]	P^a
Subjects	Male	Female		
All	10 (10-10)	11 (11-12)	0.93 (0.91-0.96)	<.001
Age group, y				
18-44	10 (9-11)	14 (12-16)	0.75 (0.65-0.86)	<.001
45-54	11 (11-12)	13 (12-15)	0.86 (0.79-0.92)	<.001
55-64	12 (11-12)	14 (13-15)	0.86 (0.81-0.91)	<.001
65-74	10 (10-11)	11 (10-12)	0.97 (0.92-1.02)	.19
≥75	8 (7-8)	7 (7-8)	1.04 (0.99-1.10)	.15
$P_{interaction}$		<.001		
Race				
White	10 (10-10)	11 (10-11)	0.93 (0.89-0.96)	<.001
African American	8 (7-8)	9 (9-10)	0.85 (0.78-0.92)	<.001
Asian	12 (12-13)	13 (12-14)	1.00 (0.94-1.06)	.87
Hispanic	10 (10-11)	11 (10-12)	0.99 (0.92-1.07)	.79
$P_{interaction}$		.017		
Stage				
Single lesion	26 (25-27)	29 (27-31)	0.95 (0.90-1.01)	.086
Multiple tumors	13 (13-14)	14 (13-15)	0.96 (0.90-1.03)	.24
Vascular invasion	8 (8-9)	9 (9-10)	0.91 (0.87-0.95)	<.001
Metastatic disease	4 (3-4)	4 (3-4)	0.94 (0.88-1.00)	.055
$P_{interaction}$		.036		
Treatment				
None or unknown	7 (6-7)	7 (7-7)	0.96 (0.93-0.99)	.017
Liver-directed therapy	27 (25-28)	27 (25-30)	0.99 (0.89-1.09)	.82
Surgical resection	44 (40-46)	48 (44-54)	0.87 (0.78-0.96)	.008
Liver transplantation	60[b]	60[b]	1.06 (0.86- 1.29)	.60
$P_{interaction}$		.045		

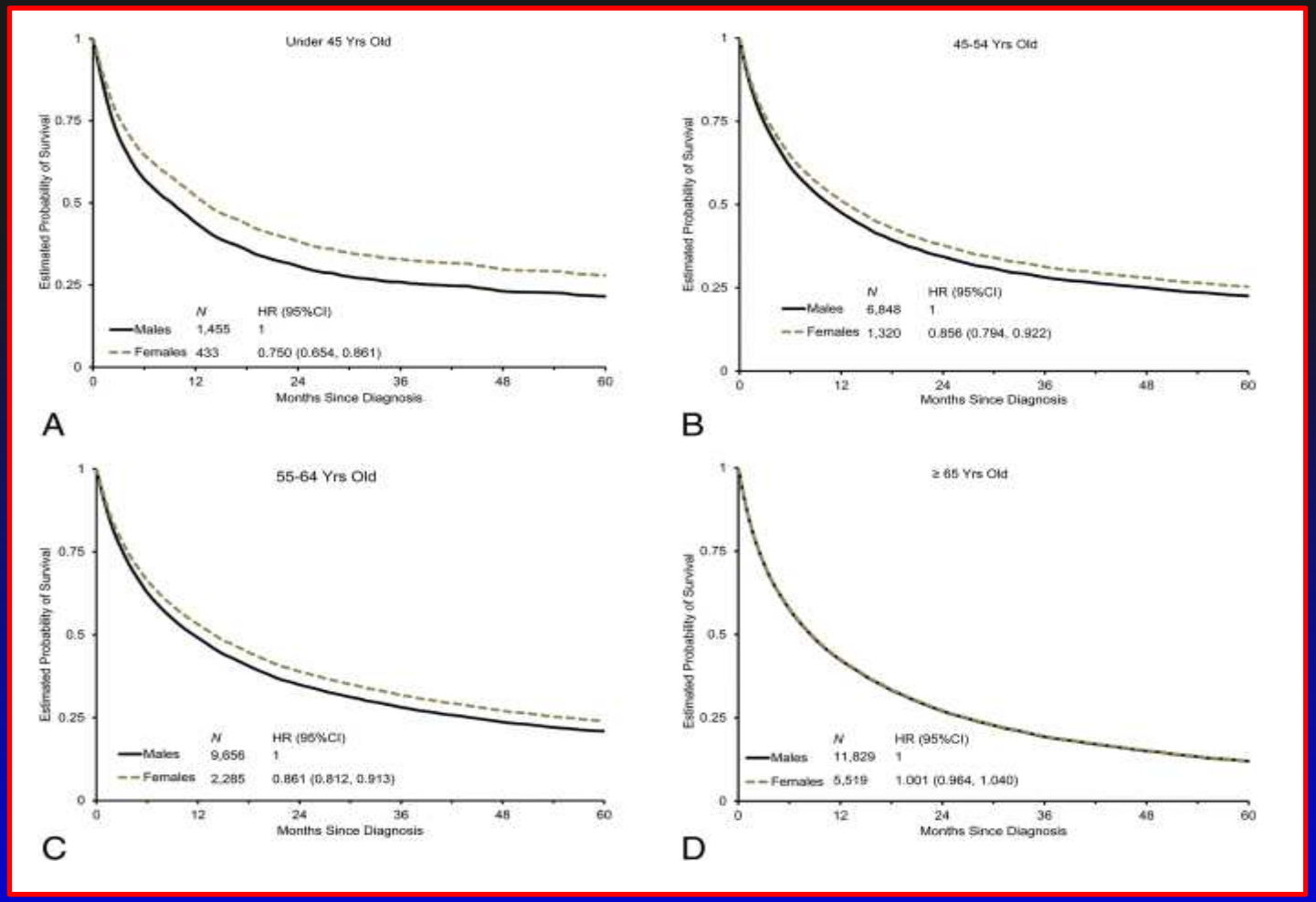
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; OS, overall survival.

[a] Men as the reference group (HR, 1).

[b] Estimates were not reached.

Yang et al., Cancer 2014

Impact of sex on the survival of patients with hepatocellular carcinoma: A Surveillance, Epidemiology, and End Results analysis



Yang et al. Cancer 2014

Impact of NAFLD

- Up to 30% of the US population has fatty liver disease: the “hepatic manifestation” of metabolic syndrome
- This can progress to inflammation, known as non-alcoholic steatohepatitis (NASH)
- NASH contributes to up to a third of HCCs in this country, and incidence is increasing
- Those with features of metabolic syndrome also have worse outcomes from several kinds of cancer

Siegel et al, Cancer 2009 115:5651-5661

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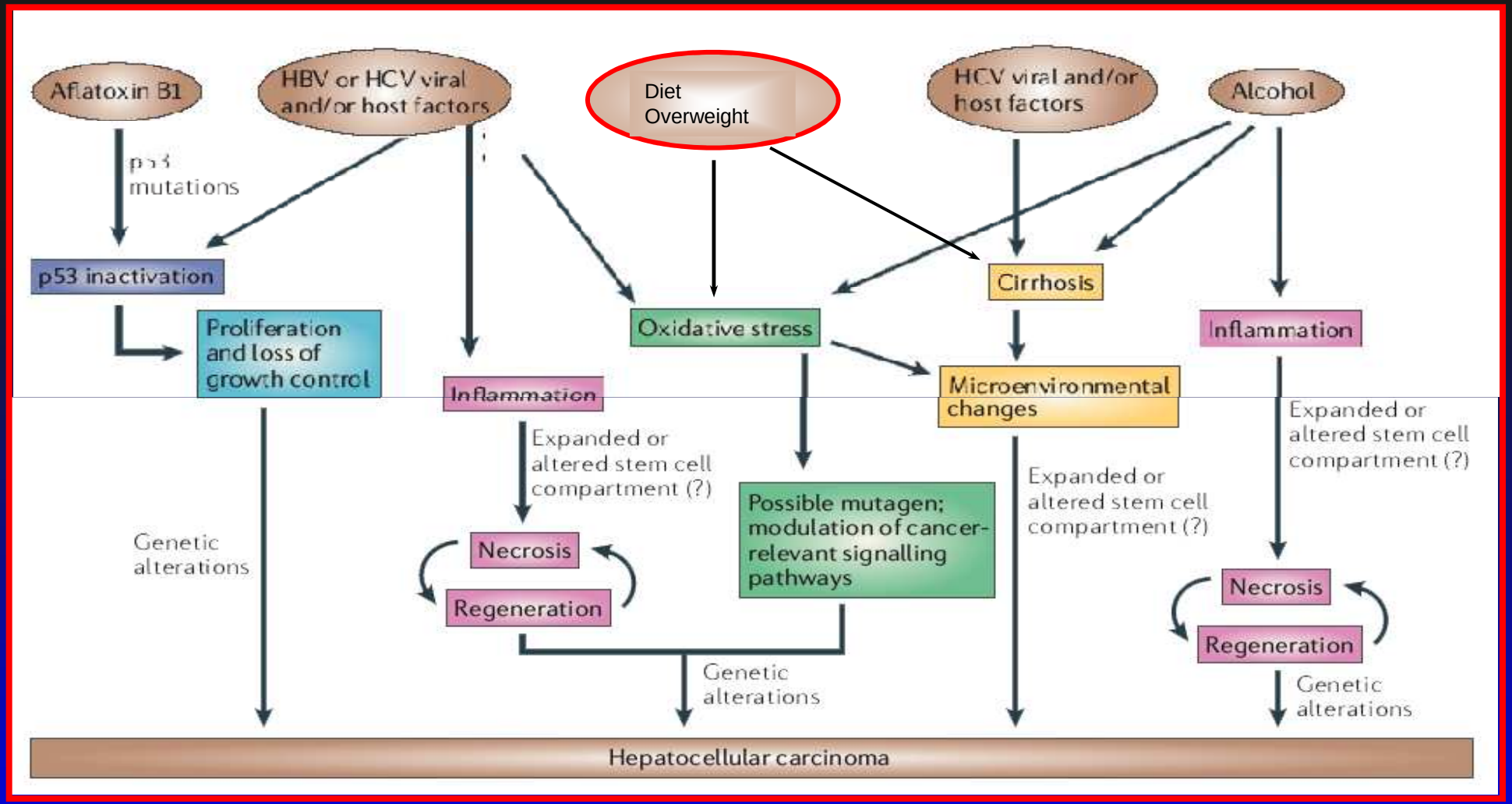
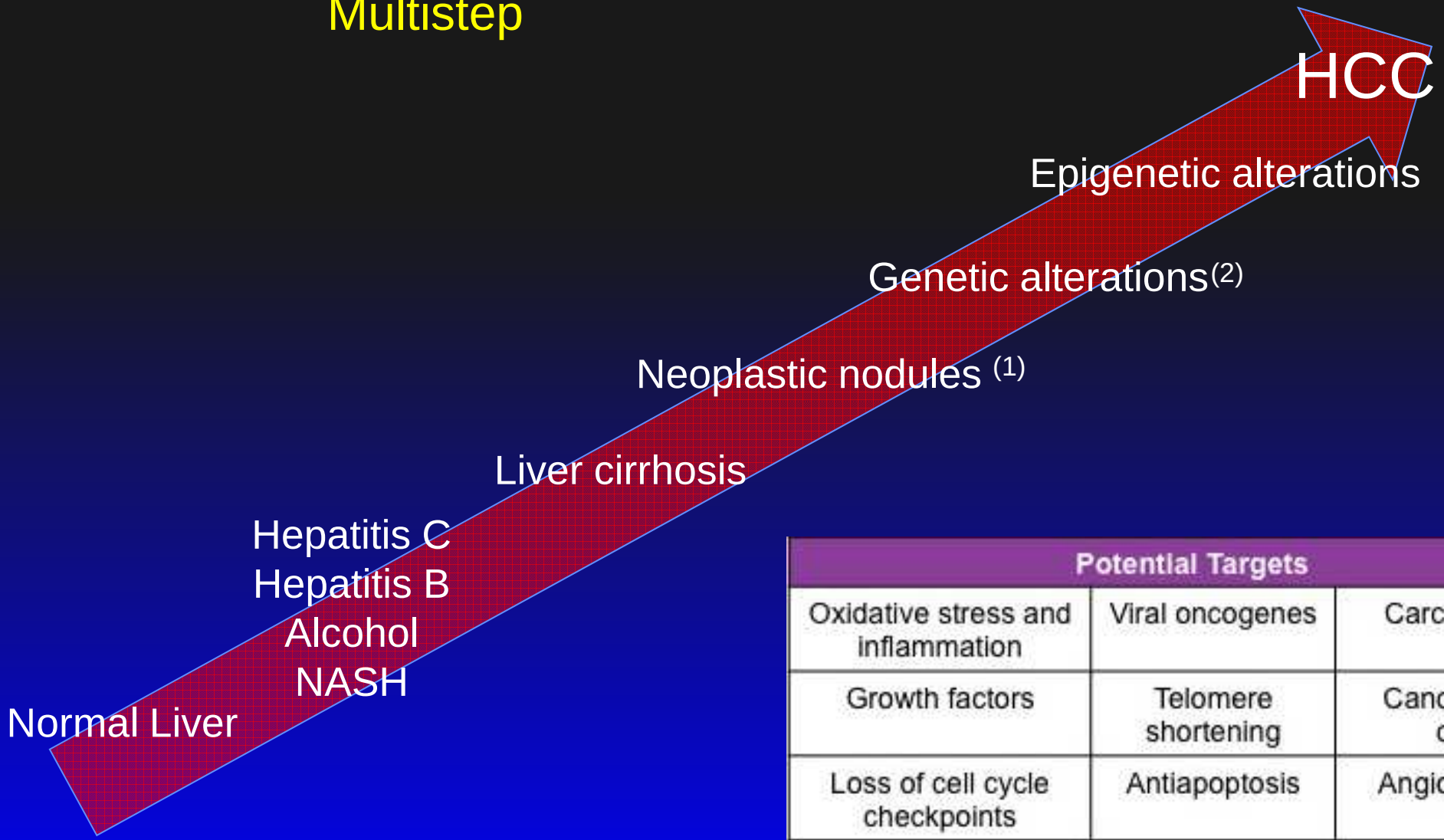
Mechanisms of hepatocarcinogenesis



Modified from Farazi , 2006)

Malignant Transformation

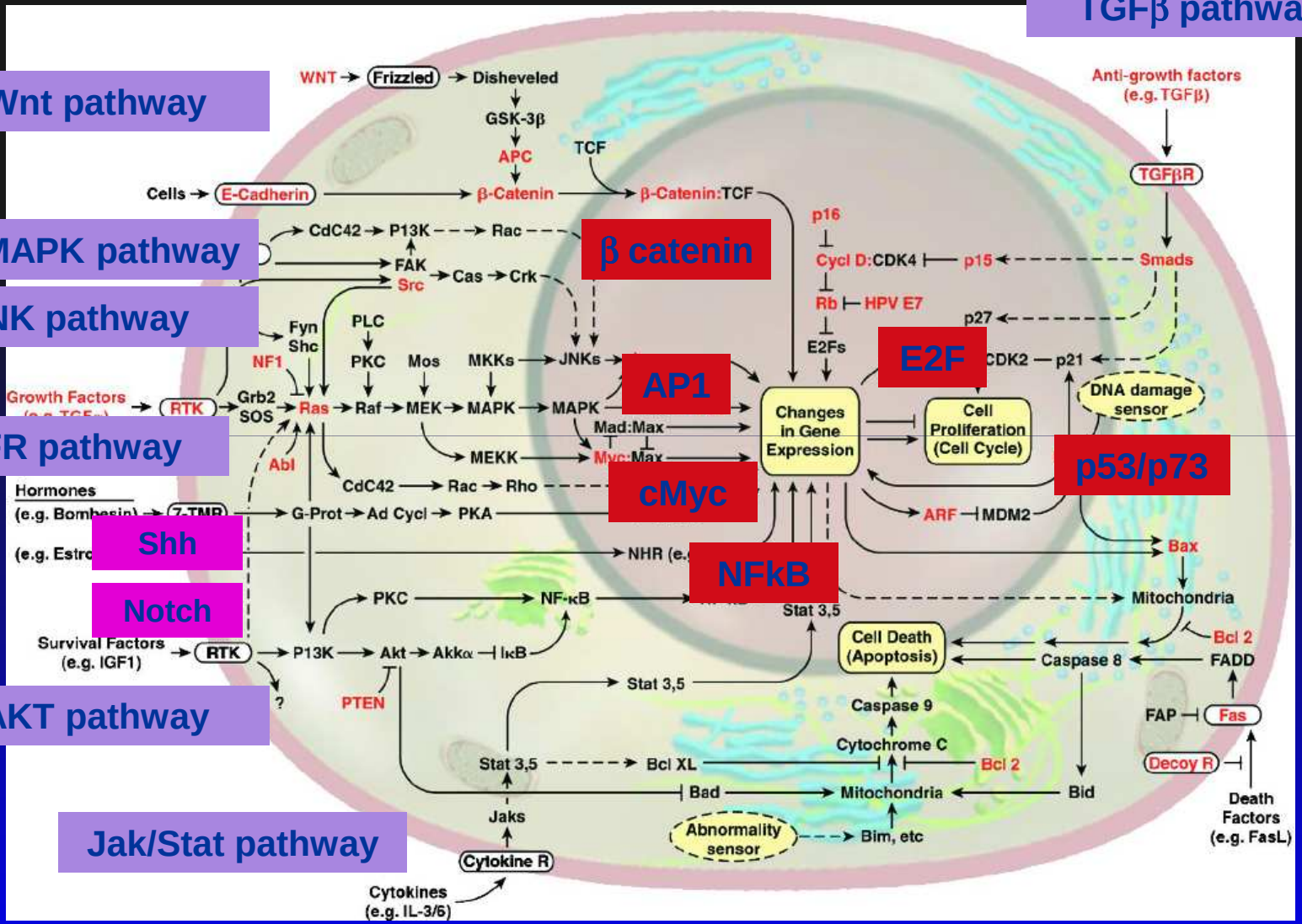
Multistep



Potential Targets		
Oxidative stress and inflammation	Viral oncogenes	Carcinogens
Growth factors	Telomere shortening	Cancer stem cells
Loss of cell cycle checkpoints	Antiapoptosis	Angiogenesis

1.Tornillo L, et al. Lab Invest 2002; 2) Verslype C eta al. AASLD 2007

Different Therapeutic Targets in Human HCCs



HCC: Pathogenesis

Liver carcinogenesis is typically a stepwise process

- Sequential genetic mutations
- Oncogene activation
- Tumor suppressor gene inactivation

No dominant pathways of hepatocellular carcinogenesis have yet been identified

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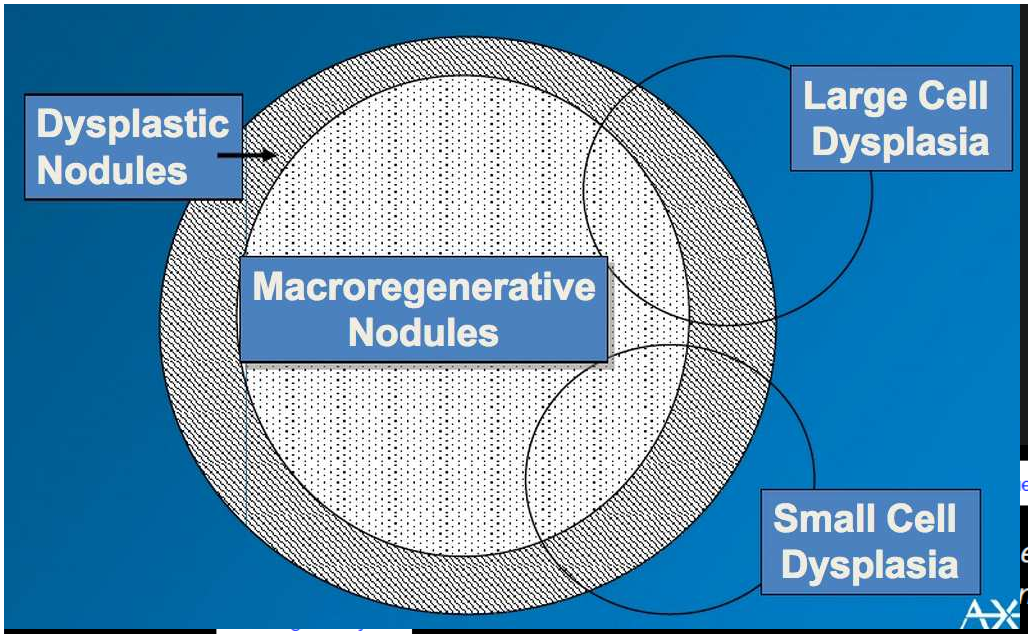
Diagnosis

Patient workup:

- ⇨Imaging: CT, MR
- ⇨Biopsy
- ⇨*Angiography*



Definite | Probable | Neither definite nor probable

No ← Mass? → Yes → Non-HCC malignancy? → Yes → OM

No → Tumor in vein? → Yes

No

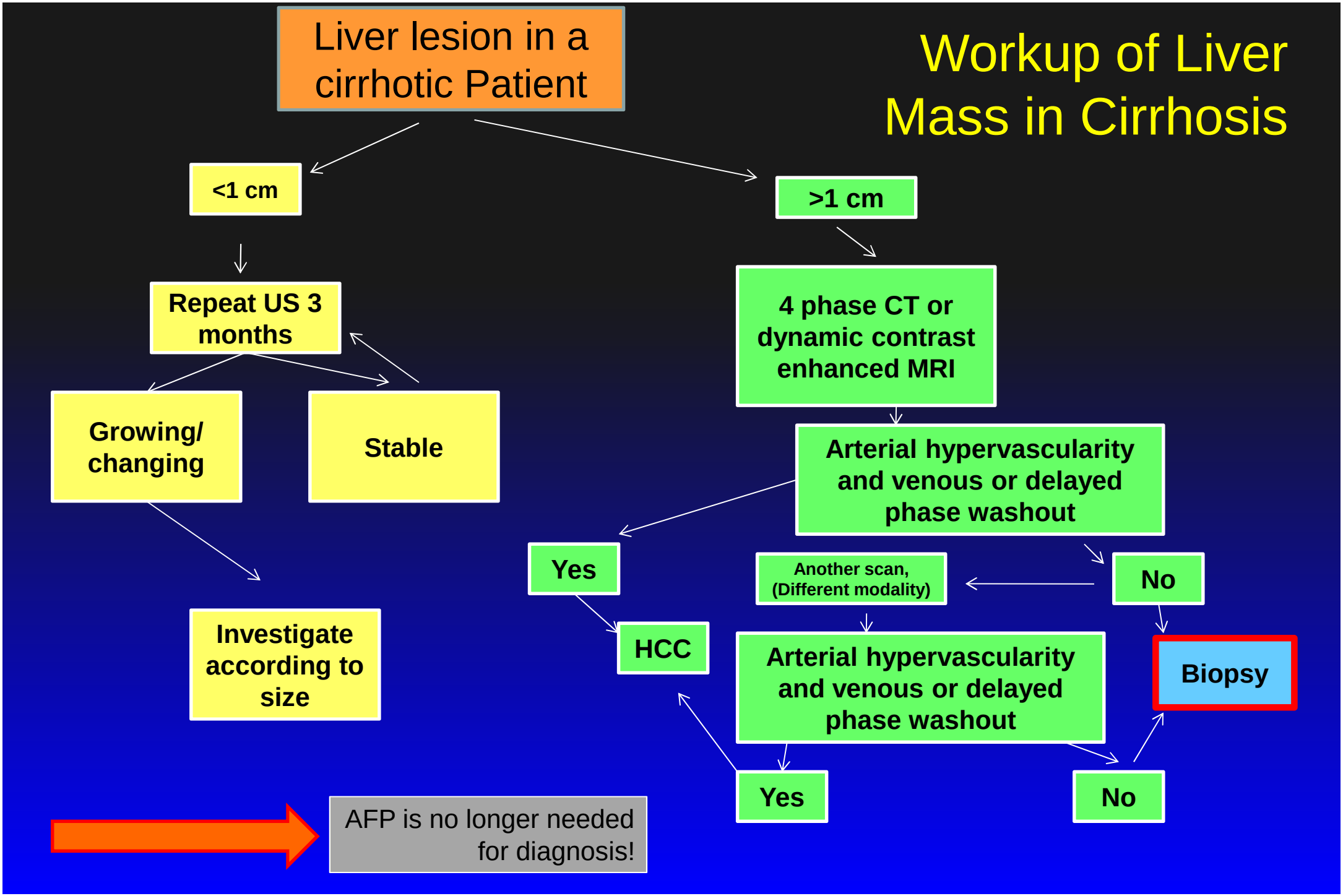
		Arterial phase hypo- or iso-enhancement		Arterial phase hyper-enhancement		
Diameter (mm):		< 20	≥ 20	< 10	10-19	≥ 20
•"Washout" •"Capsule" •Threshold growth	None:	LR3	LR3	LR3	LR3	LR4B
	One:	LR3	LR4B	LR4A	LR4A	LR5B
	≥ Two:	LR4A	LR4B	LR4A	LR5A	LR5B

LR1 | LR2 | LR3 | LR5V

LR5 Treated

Apply Ancillary Features and then Tie-Breaking Rules to Adjust Category

LR-1	Definitely benign
LR-2	Probably benign
LR-3	Intermediate probability for HCC
LR-4	Probably HCC
LR-5	Definitely HCC
LR-5V	Definitely HCC with Tumor in Vein
LR-M	Malignant, not necessarily HCC


Workup of Liver Mass in Cirrhosis
Liver lesion in a cirrhotic Patient
<1 cm
>1 cm
Repeat US 3 months
Growing/ changing
Stable
Investigate according to size
4 phase CT or dynamic contrast enhanced MRI
Arterial hypervascularity and venous or delayed phase washout
Yes
No
Another scan, (Different modality)
HCC
Arterial hypervascularity and venous or delayed phase washout
Biopsy
Yes
No
AFP is no longer needed for diagnosis!

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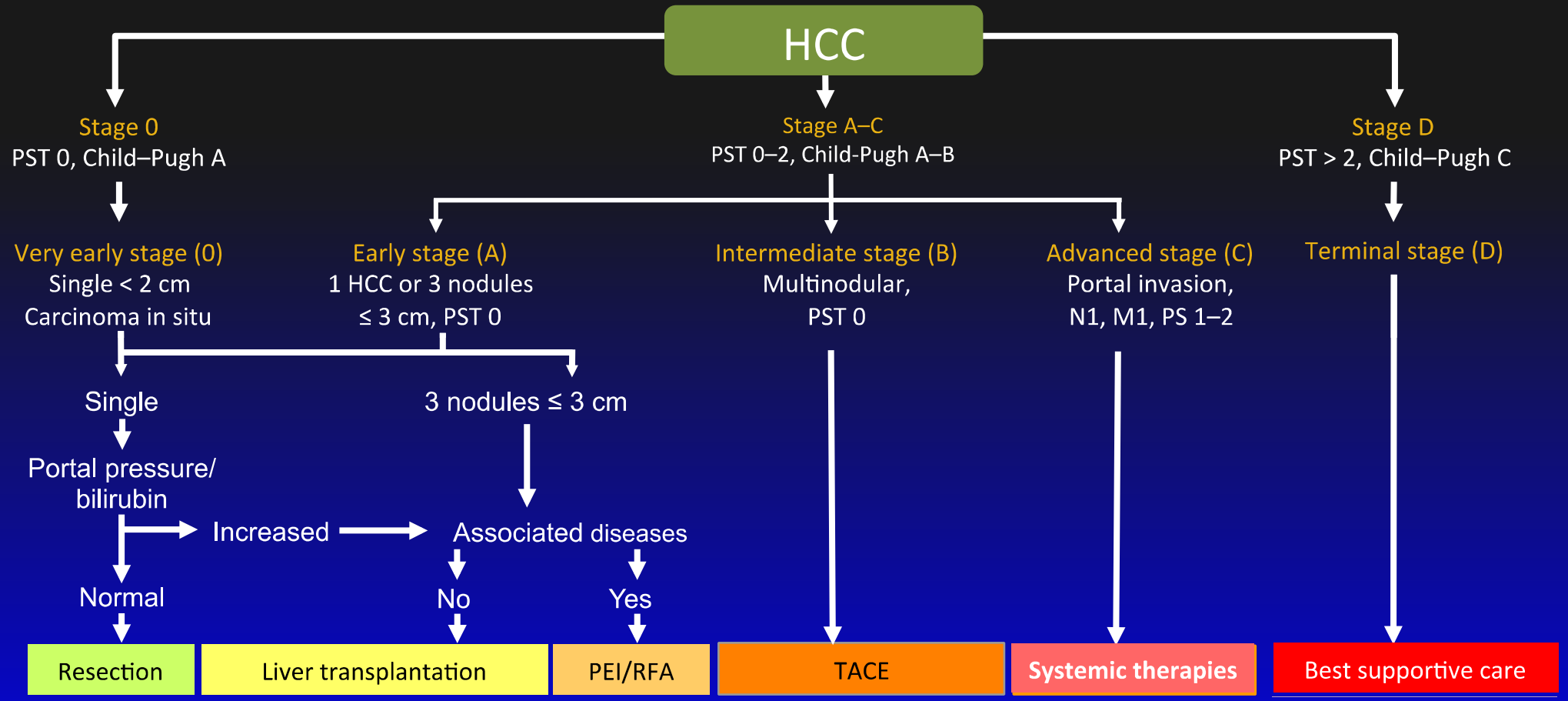
EASL-EORTC Clinical Practice Guidelines: BCLC Staging System and Treatment Strategy



PEI = percutaneous ethanol injection;
PST = Performance Status test; RFA = radiofrequency ablation.

EASL-EORTC Clinical Practice Guidelines: Management of HCC.
J Hepatol 2012;56:908–943

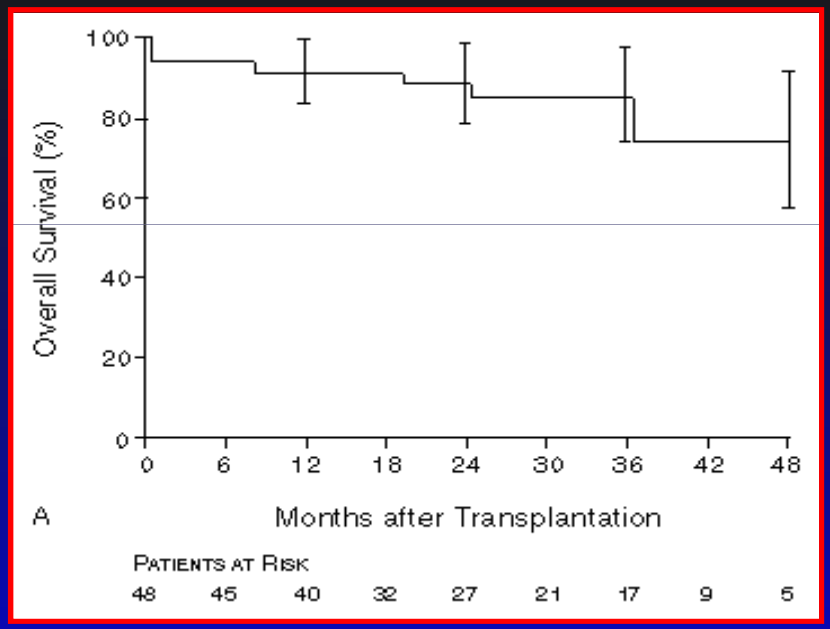
Management of HCC

- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative

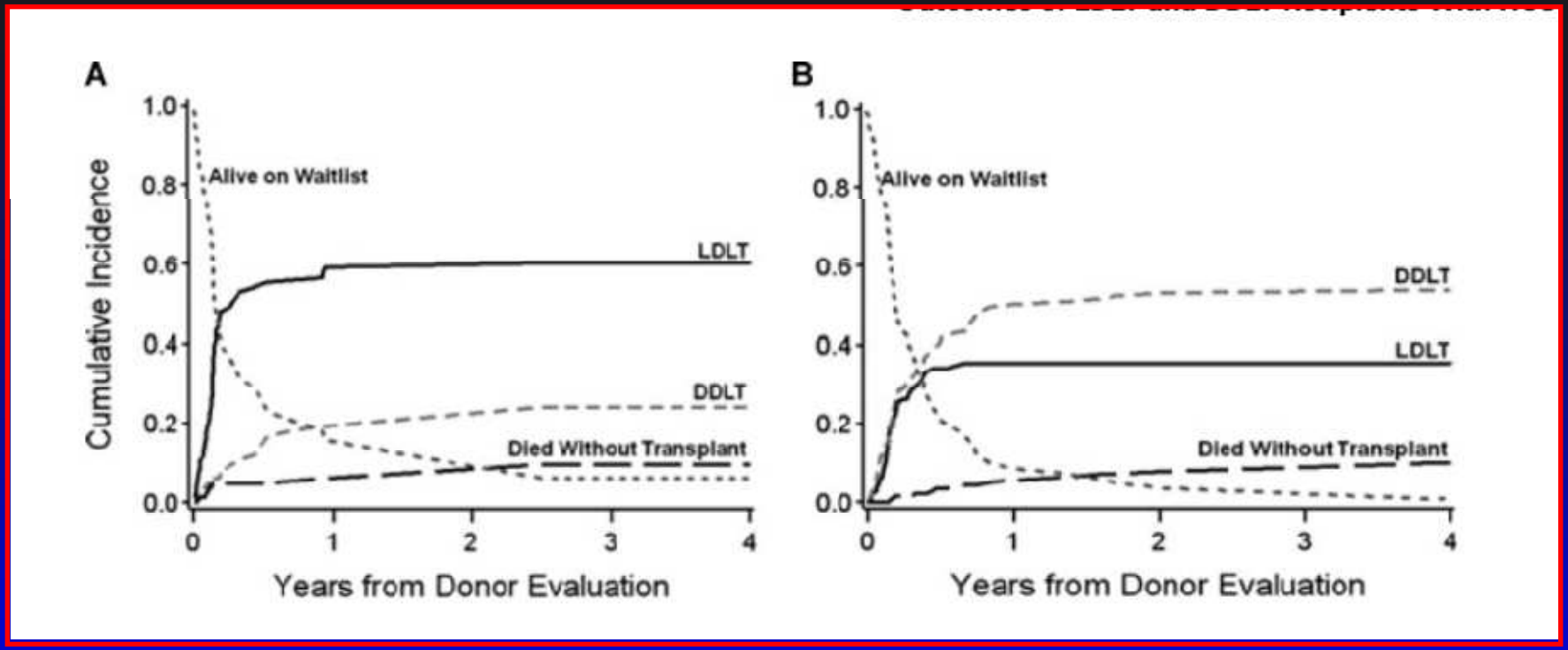
Milan Criteria for Liver Transplantation

- If only one tumor, it must be 5 cm or less
- 3 or fewer tumors, each 3 cm or less
- No gross vascular invasion



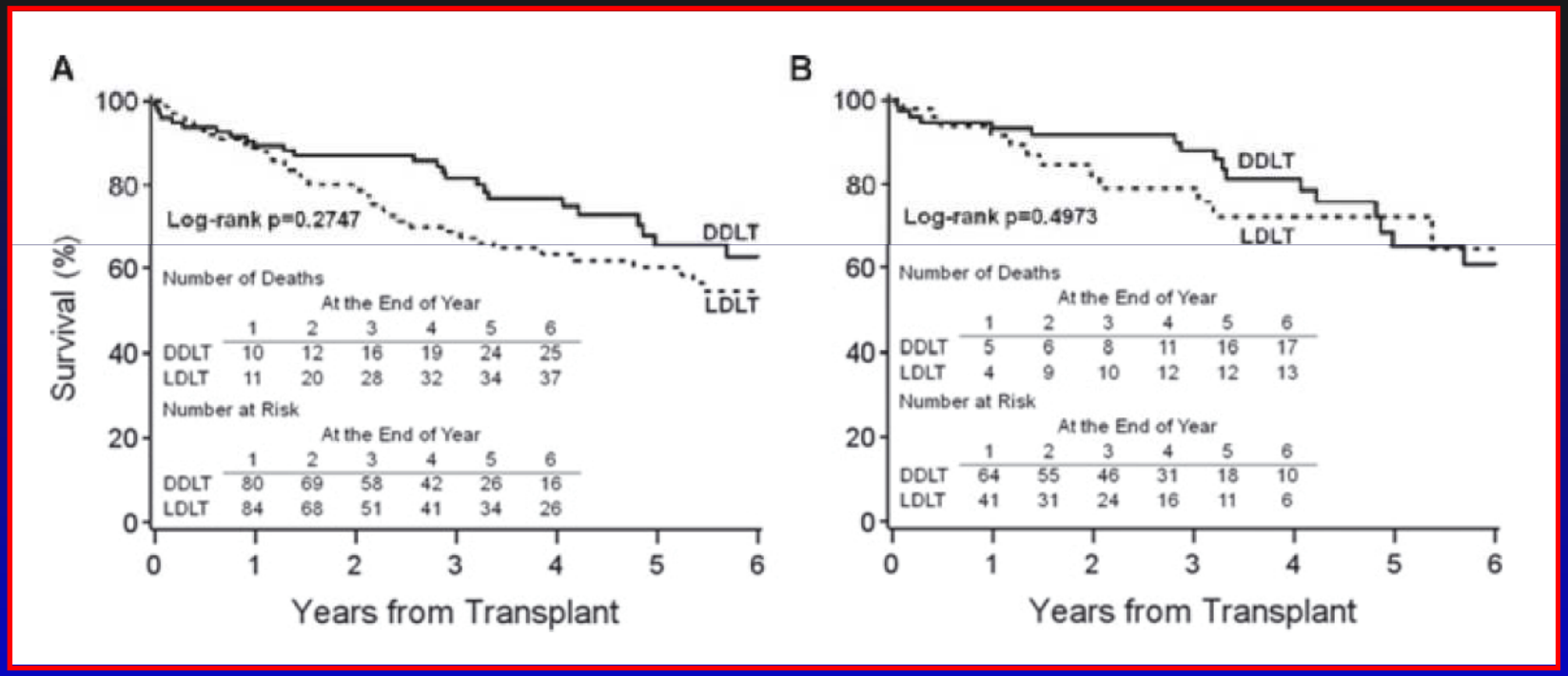
Mazzafero et al. NEJM 1996, 334:693-700

Cumulative probability over time of LDLT, DDLT, remaining alive on the waitlist and death without transplant, from the 1rst living donor evaluation for (A) HCC pts in the pre-MELD and (B) HCC pts in the MELD era



Kukik et al., AJT 2012

Unadjusted probability of patient survival by time since LDLT or DDLT for (A) all HCC pts and (B) HCC pts in the MELD era



Kukik et al., AJT 2012

Resection

Consider resection in:

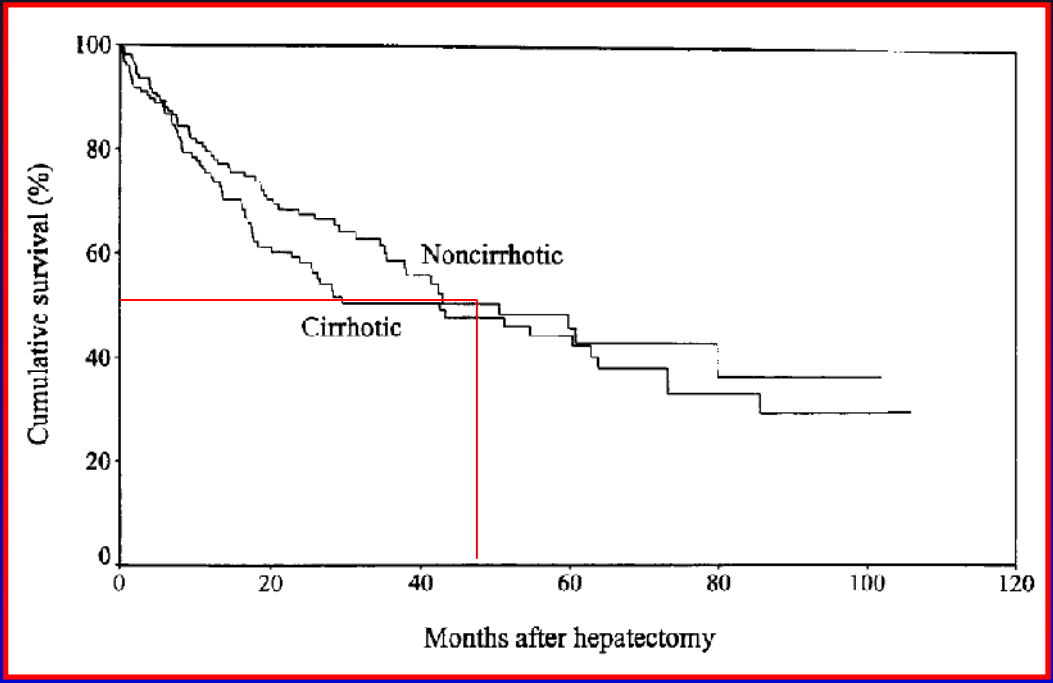
- Non-cirrhotics (often those with HBV!)
- Compensated cirrhotics (normal bili and hepatic venous pressure gradient <10 mm Hg)
- Only 10-20% of those in the West are candidates for resection

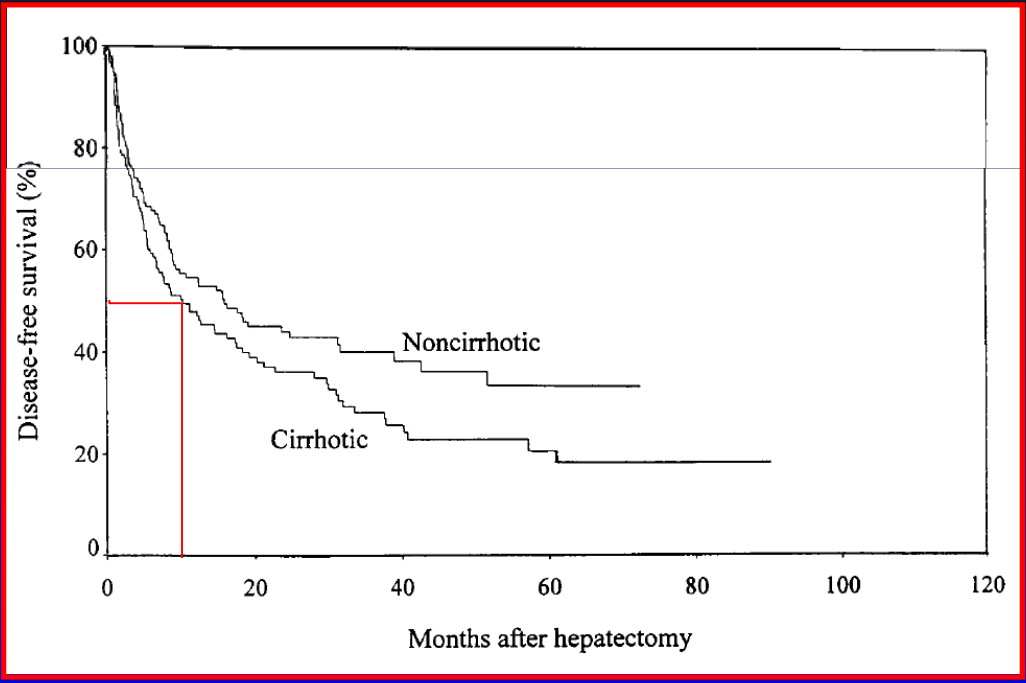
However, in patients with underlying cirrhosis

- Careful patient selection,
- Meticulous intraoperative technique
- Extremely careful perioperative management,

are mandatory otherwise liver resection is associated with a significant risk of postoperative morbidity and/or mortality.

Cumulative and Disease-free Survival Curves after Resection of HCC in Cirrhotic and Non-Cirrhotic Patients.





Poon et al., JCO 2000

Chemoembolization (TACE)

- The normal liver receives most of its blood supply through the portal vein, and only about 25 percent from the hepatic artery
- Tumors receive almost all of their blood supply from the hepatic artery
- “Dual therapy” using both embolization and chemotherapy
- Now also using Y90: radiolabeled beads

Outcome of TACE

HCC

1 year survival	54-88%
2 year survival	33-64%
3 year survival	18-51%
5 year survival	<6%

In general the outcome is hard to quantify in a meta-analysis as many different protocols are used by different groups

Review of TACE

- Overall survival advantage seen with chemoembolization
- Approximately ½ the risk of death with two year follow up
- Response rates in 35% of patients
- Highly selected patients

Llovet and Bruix, Hepatology 2003; 37:429-422

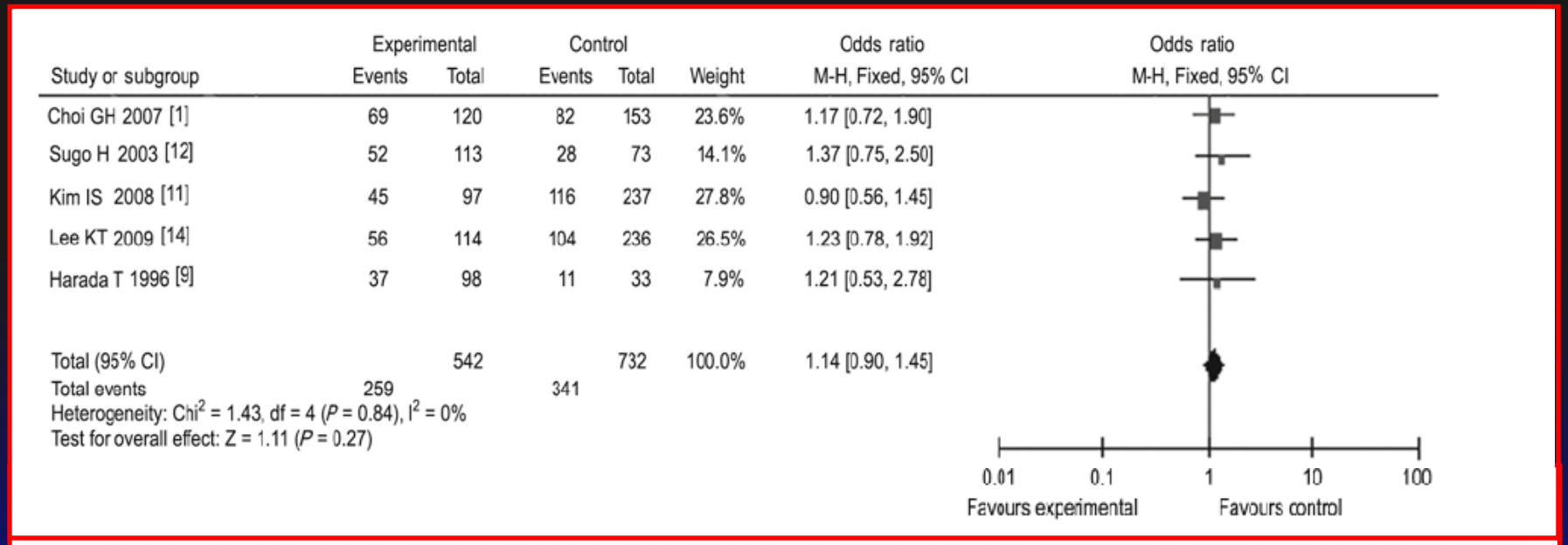
Other Local Therapies

- RFA
  - Nonrandomized data suggest outcomes as good as resection for small (<2 cm) lesions
- Percutaneous ethanol injection (PEI)
  - has been shown to produce necrosis of small HCC.
  - It is best suited to peripheral lesions, less than 3 cm in diameter

Combined therapies

The 3- and 5-year overall survival rates of TACE + liver resection versus liver resection alone

3 years



Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, Fixed, 95% CI
Choi GH 2007 [1]	69	120	82	153	23.6%	1.17 [0.72, 1.90]
Sugo H 2003 [12]	52	113	28	73	14.1%	1.37 [0.75, 2.50]
Kim IS 2008 [11]	45	97	116	237	27.8%	0.90 [0.56, 1.45]
Lee KT 2009 [14]	56	114	104	236	26.5%	1.23 [0.78, 1.92]
Harada T 1996 [9]	37	98	11	33	7.9%	1.21 [0.53, 2.78]
Total (95% CI)		542		732	100.0%	1.14 [0.90, 1.45]
Total events	259		341			

Heterogeneity: $Chi^2 = 1.43$, df = 4 ($P = 0.84$), $I^2 = 0\%$

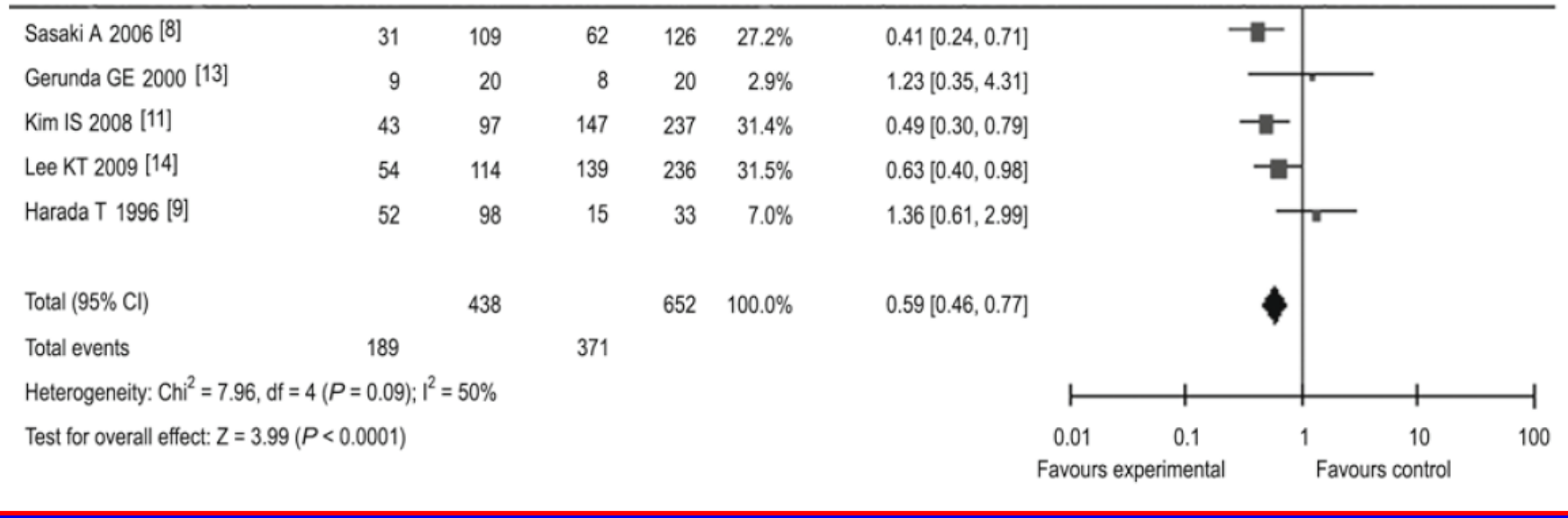
Test for overall effect: Z = 1.11 ($P = 0.27$)

Odds ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours experimental Favours control

5 years



Sasaki A 2006 [8]	31	109	62	126	27.2%	0.41 [0.24, 0.71]
Gerunda GE 2000 [13]	9	20	8	20	2.9%	1.23 [0.35, 4.31]
Kim IS 2008 [11]	43	97	147	237	31.4%	0.49 [0.30, 0.79]
Lee KT 2009 [14]	54	114	139	236	31.5%	0.63 [0.40, 0.98]
Harada T 1996 [9]	52	98	15	33	7.0%	1.36 [0.61, 2.99]
Total (95% CI)		438		652	100.0%	0.59 [0.46, 0.77]
Total events	189		371			

Heterogeneity: $Chi^2 = 7.96$, df = 4 ($P = 0.09$); $I^2 = 50\%$

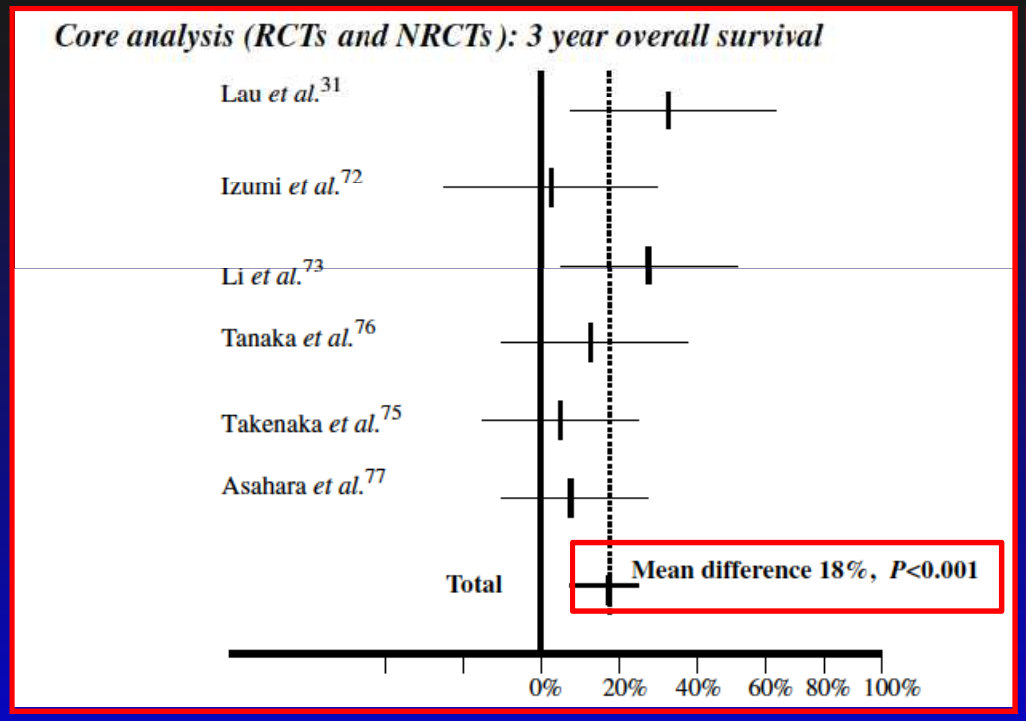
Test for overall effect: Z = 3.99 ($P < 0.0001$)

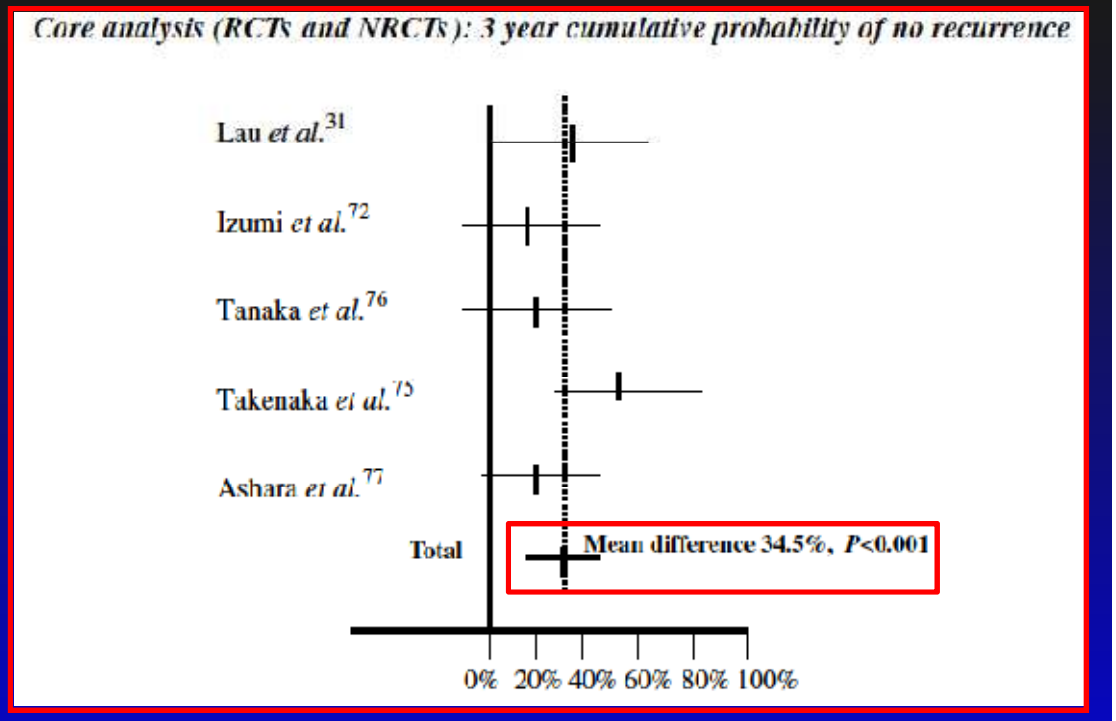
0.01 0.1 1 10 100

Favours experimental Favours control

Yu et al., 2013

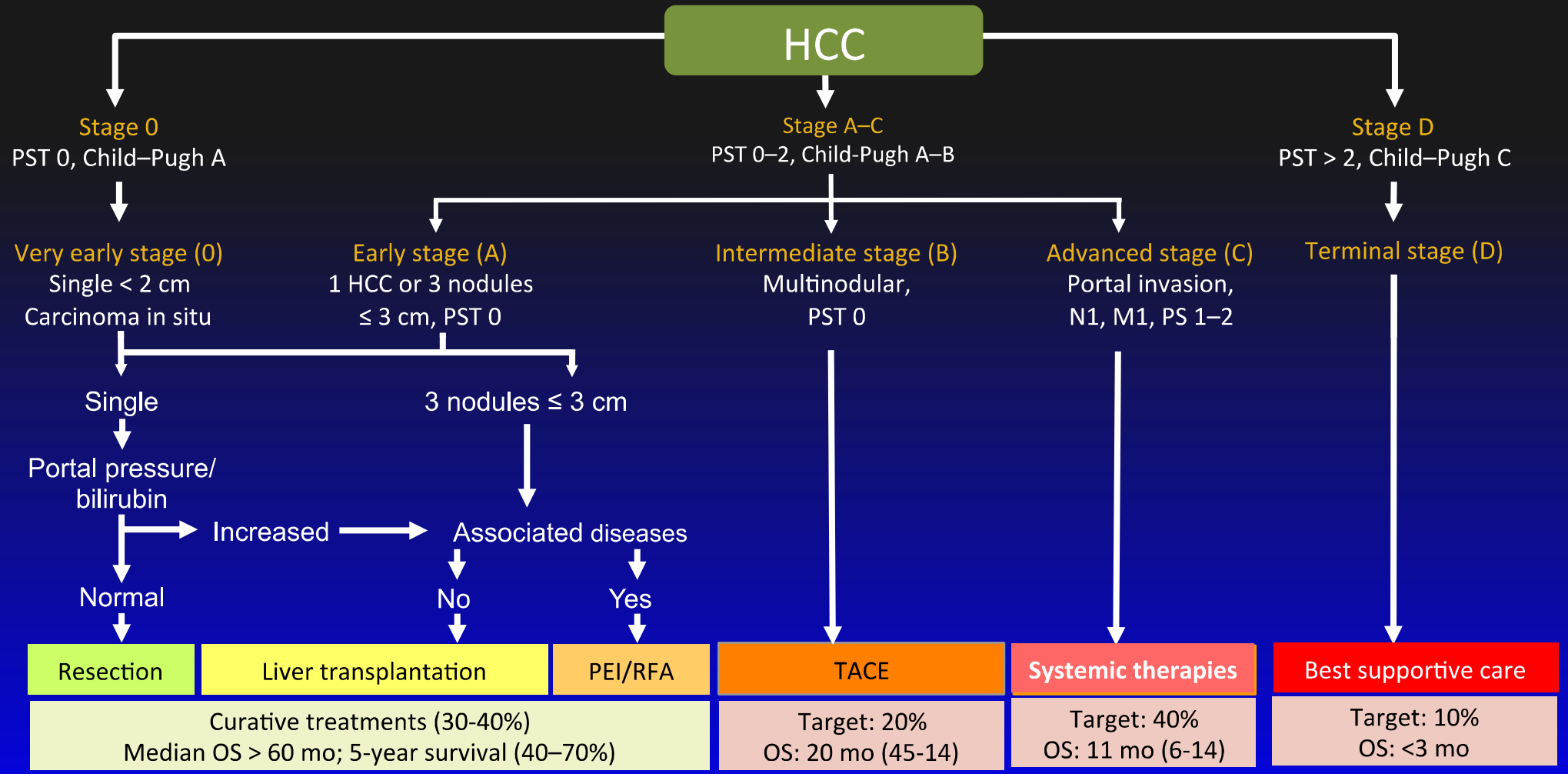
Post-operative transarterial chemotherapy: cumulative probability of overall survival and of no recurrence at 3 years





Mathurin et al., APT 2013

EASL-EORTC Clinical Practice Guidelines: BCLC Staging System and Treatment Strategy



PEI = percutaneous ethanol injection;
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EASL-EORTC Clinical Practice Guidelines: Management of HCC.
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Treatment of HCC in US non-Federal Hospitals in 2000

- Surgical Resection: 4.9%
- Liver Transplant: 1.8%
- Local Ablation: 3.5%
- Embolization: 5.5%
- Chemotherapy: 11%

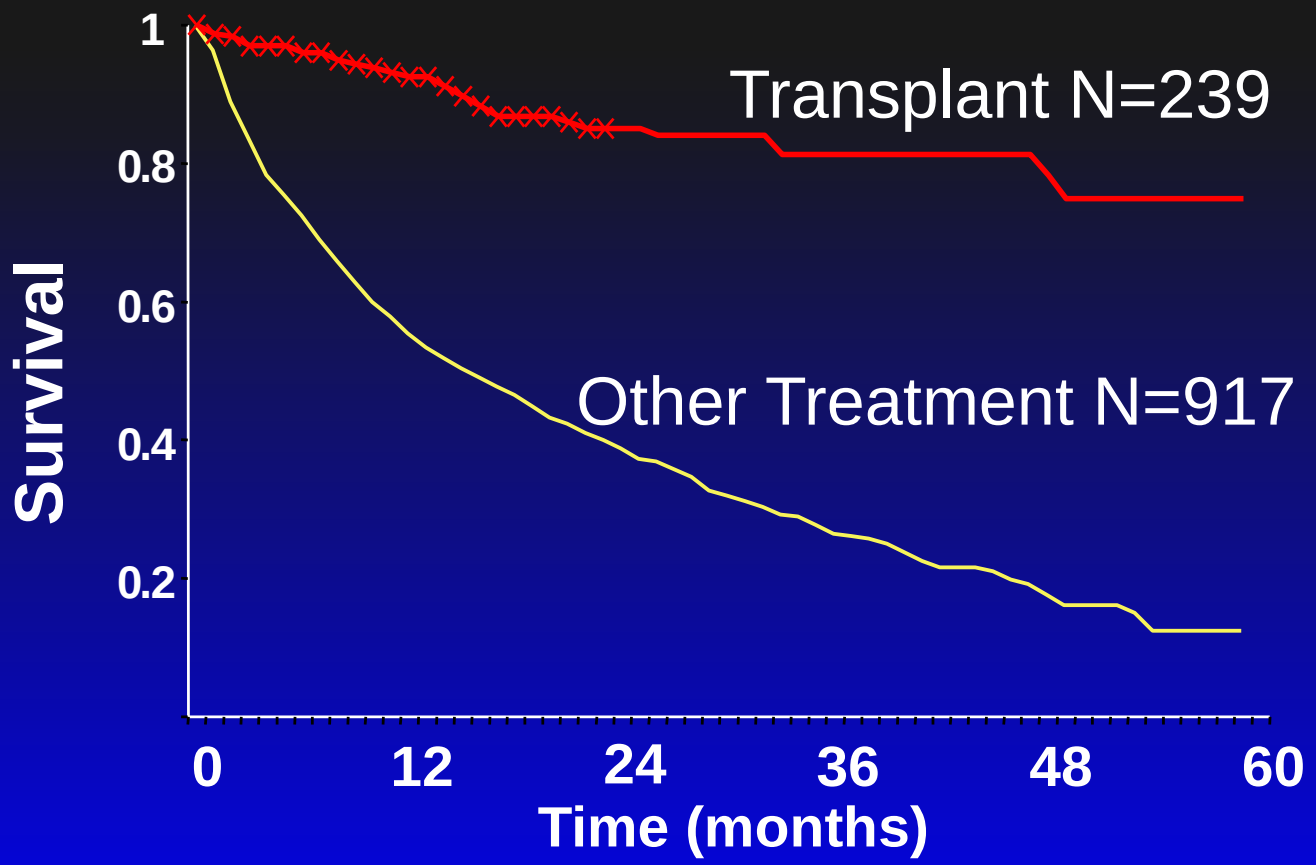
Kim WR et al. Gastroenterology 2005

Treatment for HCC Often Suboptimal

- Proportion of patients receiving potentially curative therapy
  - 34.0% of patients with single lesions
  - 34.0% of patients with lesions < 3 cm
  - 19.3% of patients with lesions > 10 cm
  - 4.9% of patients with metastatic disease
- 11.5% of patients ideal for transplantation received it
- 14.3% of patients ideal for surgical resection received it

El-Serag HB, et al. J Hepatol. 2006;44:158-166.

Survival Curves for Transplant vs. Other Treatment for Hepatocellular Carcinoma



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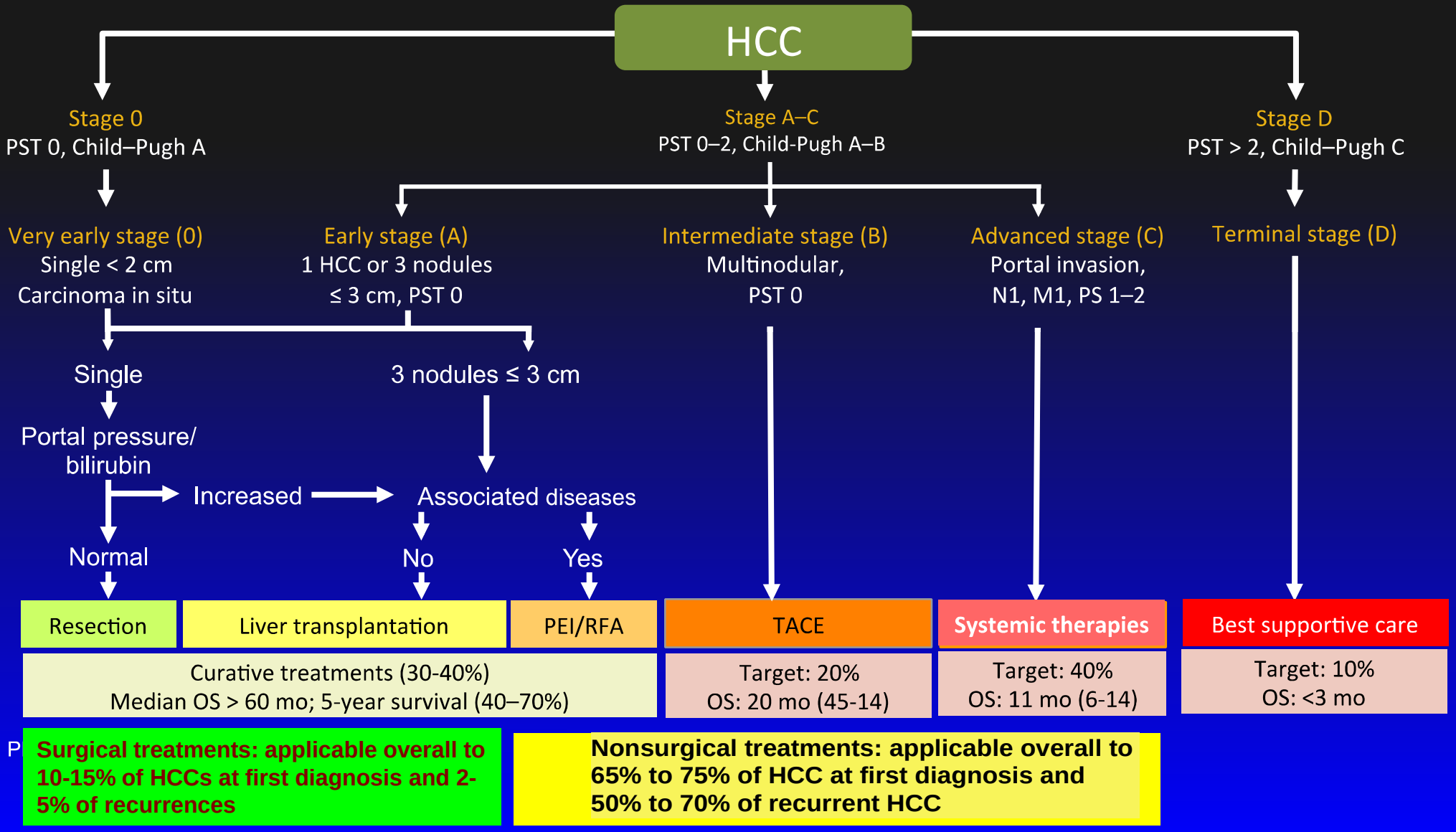
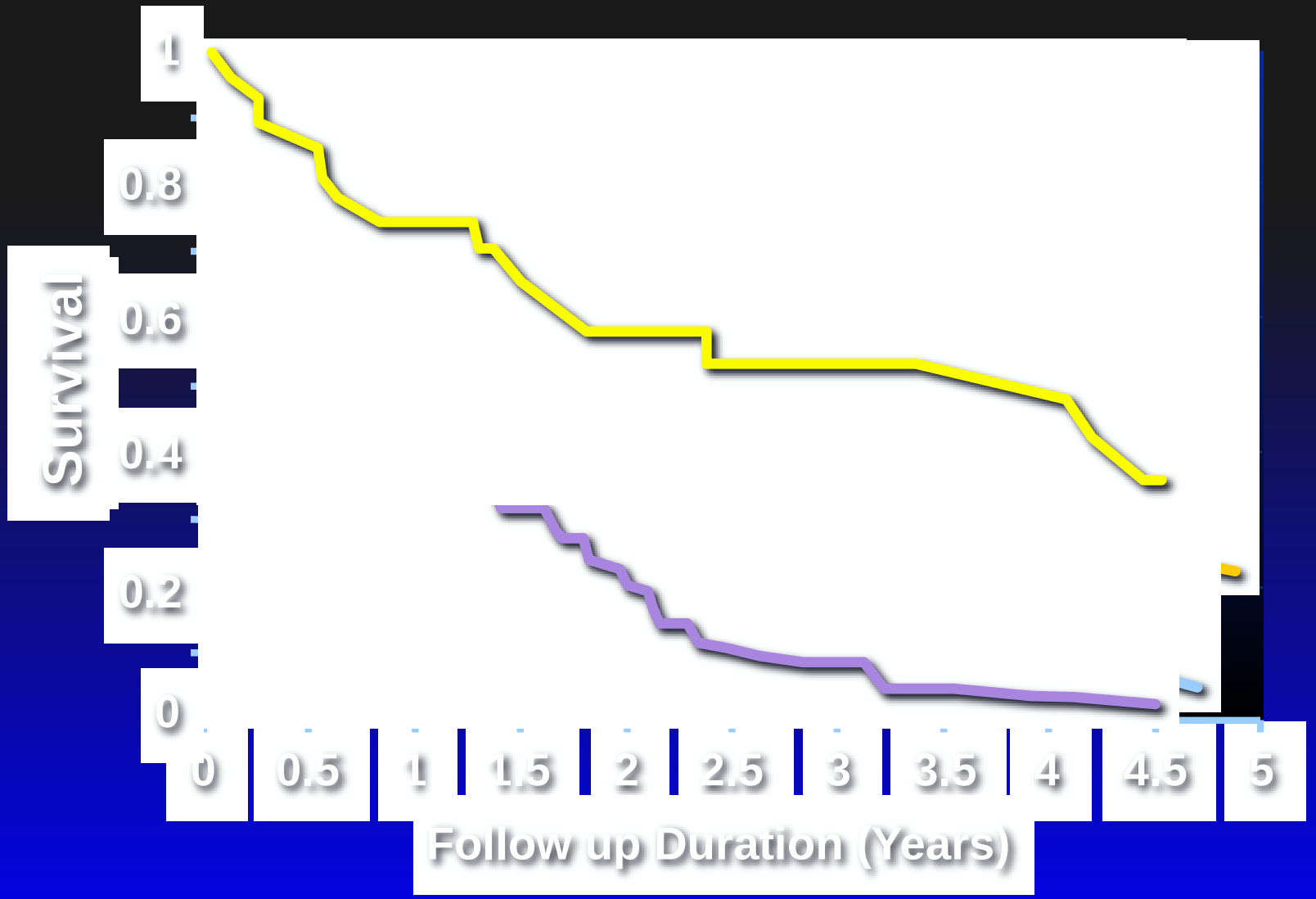


Therapeutic options

- LT: curative but insufficiently available
- Resection: satisfactory results but insufficienlty applicable
- TACE
  - accepted as treatment of choice for unresectable (nonablatable?) HCC
  - Response rates in about 35% of patients
  - Best vs good performance status, Child-Pugh class A-B
  - Metaanalyses suggest benefit in well-selected patients for embolization c/w placebo
- RFA
  - Nonrandomized data suggest outcomes as good as resection for small (<2 cm) lesions
- PEI is for developing countries with limited resources

Outcomes of HCC Treatment

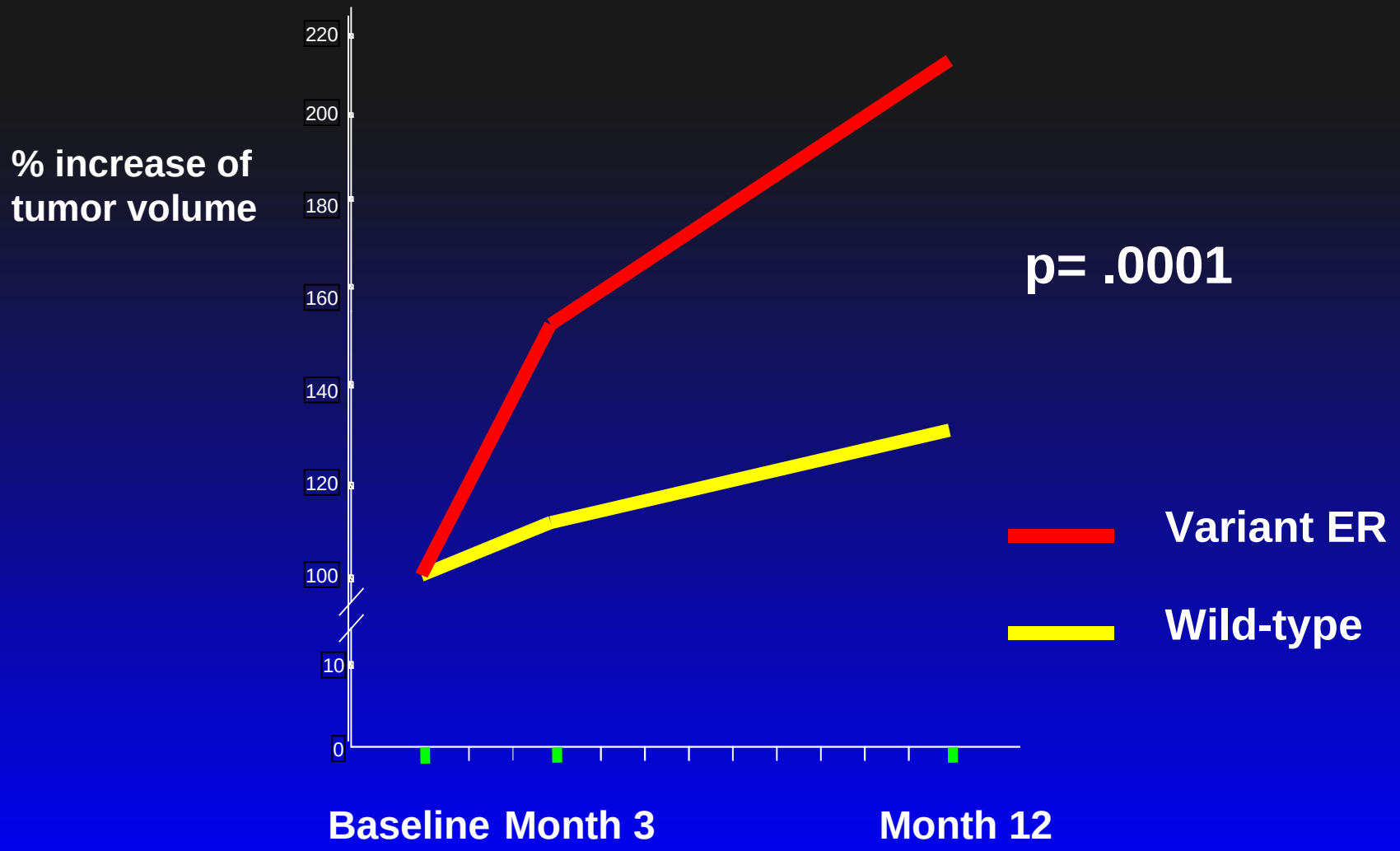


El-Serag HB et al J Hepatology 2006

HCC aggressiveness

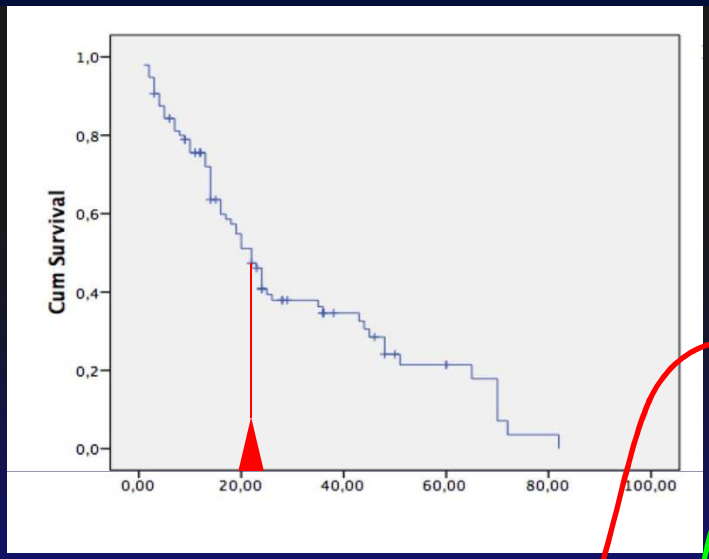
- differentation
- vascular invasion
- growth

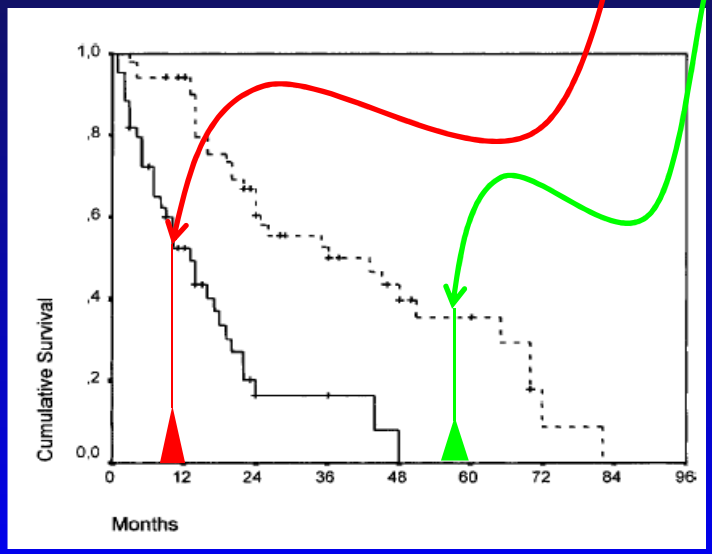
Percent increment of tumor mass at months 3 and 12



Villa et al. Hepatology 2000

Cumulative survival in 96 patients with inoperable HCC





Death occurred in 68 of 96 patients (70.8%).

Causes of death

Massive invasion of the liver by the tumor	20	(29.4%)
Slowly progressive liver failure due to underlying cirrhosis	29	(48.6%)
Upper gastrointestinal bleeding	7	(10.3%)
Ill-defined (sepsis)	12	(17.6%)

A statistically significant correlation between progression of disease at year 1 and cause of death was present, with patients with slower progression dying more often from gradual liver impairment ($P < .0215$).

Hepatology 2000

Outline

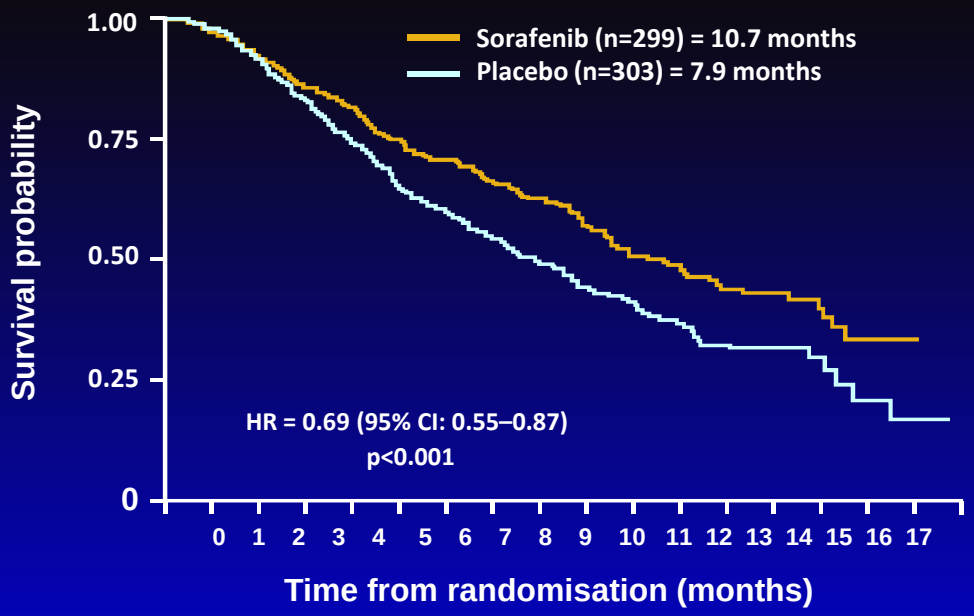
- Definition
- Epidemiology
- Biology
- Diagnosis/Prognosis/Management
- Current Therapies
- Future of Targeted Therapy

Sorafenib

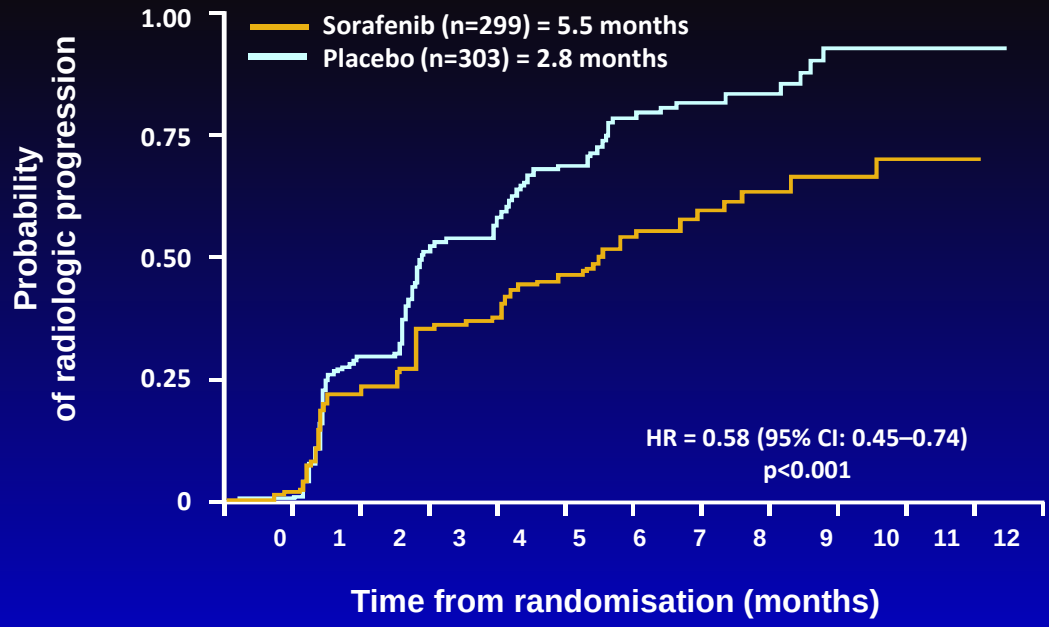
- Small molecule, orally administered
- Multi-kinase inhibitor
- Inhibits tumor-cell proliferation and tumor angiogenesis
  - Inhibits molecular components of the Raf-MEK-ERK signaling pathway, thus inhibiting tumor growth
  - Inhibits the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR- β), thus inhibiting neoangiogenesis

SHARP Phase III Trial in Advanced HCC: Results

Overall Survival



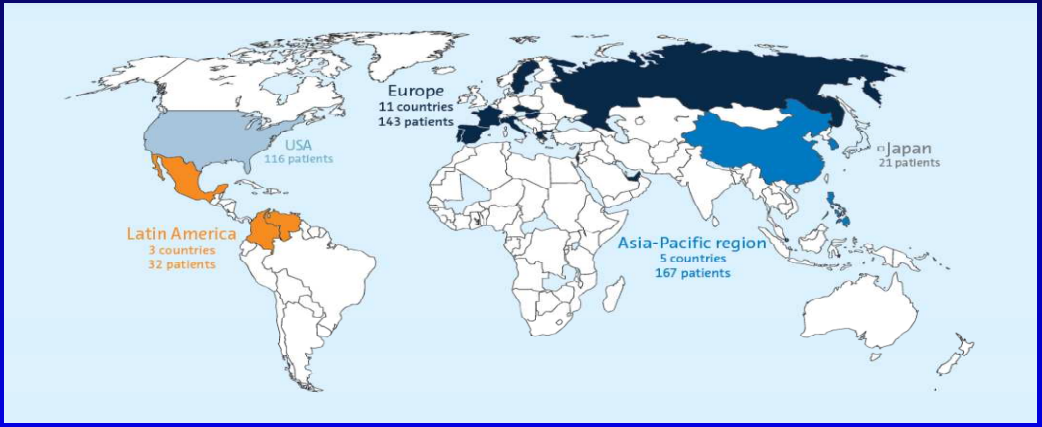
Time to Progression
(independent central review)



Llovet JM, et al. N Engl J Med 2008; 359: 378-90

Field practice – GIDEON study

- GIDEON is a global, prospective, non-interventional study that is assessing the use of sorafenib in patients with unresectable HCC within real-life clinical practice
  - GIDEON recruited >3000 patients from >350 sites in 39 countries
  - First patient in 2009 – last patient in April 2011
- The first interim analysis includes preliminary evaluation of sorafenib use in 500 patients
- The second interim includes 1500 patients
- The final analysis is planned 12 months after enrolment of the 3000th treated patient



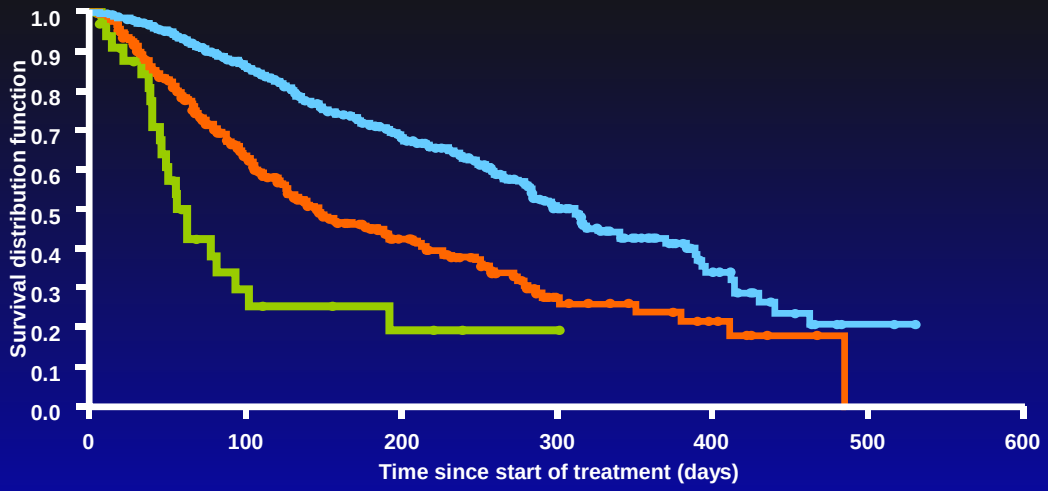
Lencioni et al. Int J Clin Pract. 2012 Jul;66(7):675-83

GIDEON 2nd interim analysis: OS by Child-Pugh (A) and BCLC (B) status at study entry

C-P A (<7) (*n*=984), median (95% CI) 312 (284, 341) days
10.3 months

C-P B (7-9) (*n*=376), median (95% CI) 147 (126, 189) days
4.8 months

C-P C (>9) (*n*=36), median (95% CI) 62 (46, 94) days
2.0 months



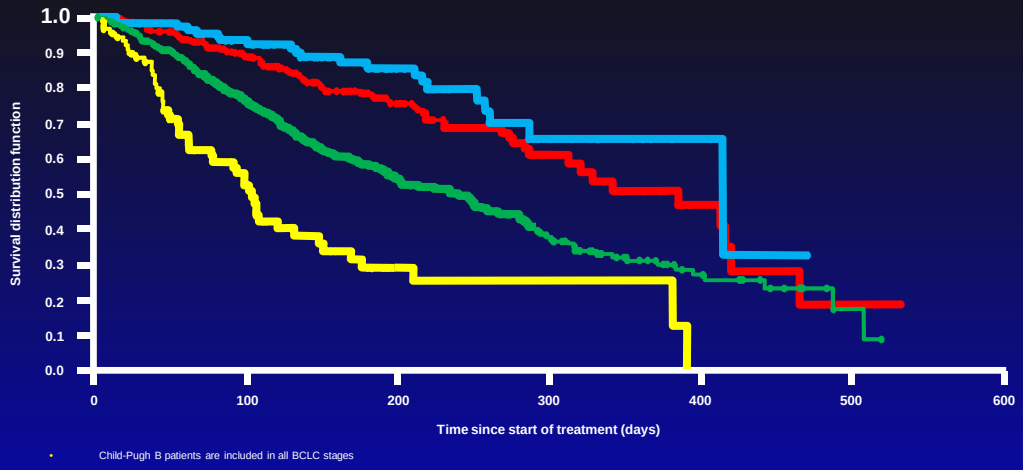
(A)

Stage A (*n*=117), median (95% CI) 413 (413, NE) days
13.6 months

Stage B (*n*=311), median (95% CI) 384 (312, 419) days
12.6 months

Stage C (*n*=877), median (95% CI) 240 (198, 260) days
7.9 months

Stage D (*n*=93), median (95% CI) 104 (77, 148) days
3.4 months



(B)

[a]207 patients not evaluable
CI, confidence interval

Marrero JA, et al. *J Clin Oncol*. 2011;29(suppl): Abstract 4001.

Field practice - GIDEON study: Safety profile as per 2nd interim analysis

- Disease progression, AE, and deterioration of general condition are major reasons for discontinuation of sorafenib
- Median time from initial diagnosis to Sor initiation was longer in Japan (30 mos) than in other regions (1-3 mos), as was median time from diagnosis to death (100 mos, Japan; 16-37 mos, other regions).
- Regional variations in Sor use were observed. The US and Japan had the lowest median daily doses and the most dose modifications.
- AE profiles were comparable between subgroups of Child-Pugh status.
- A lower initial sorafenib dose of 400 mg/day did not appear to alter AE profiles compared with an initial dose of 800 mg/day. AEs that required discontinuation of sorafenib were various, with a relatively low incidence for each AE in the overall population

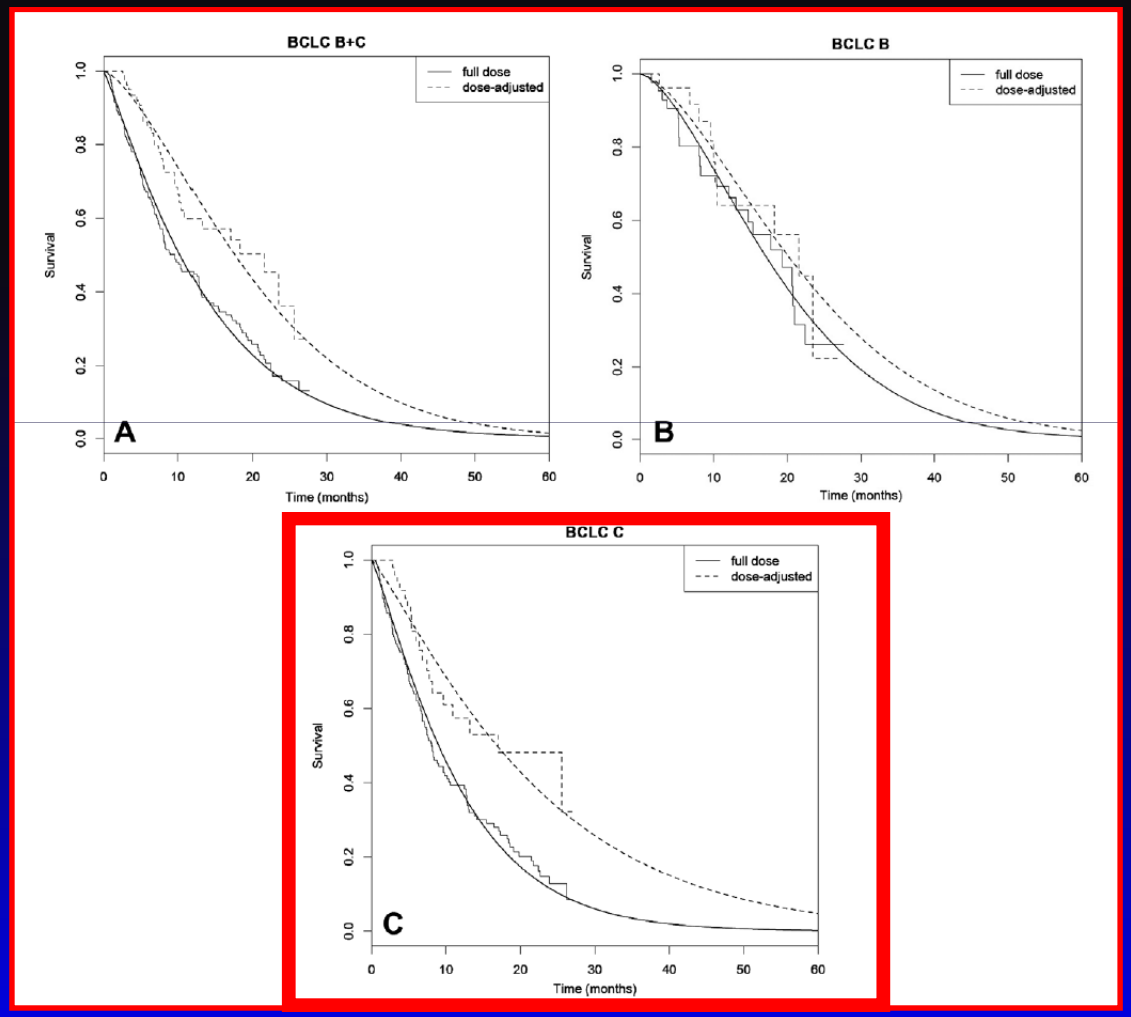
Marrero JA, et al. *J Clin Oncol*. 2011;29(suppl): Abstract 4001.

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Cost-Effectiveness of Sorafenib Treatment in Field Practice for Patients With Hepatocellular Carcinoma

Calogero Cammà,[1] Giuseppe Cabibbo,[1] Salvatore Petta,[1] Marco Enea,[2] Massimo Iavarone,[3] Antonio Grieco,[4] Antonio Gasbarrini,[4] Erica Villa,[5] Claudio Zavaglia,[6] Raffaele Bruno,[7] Massimo Colombo,[3] and Antonio Craxì[1] on behalf of the WEF and the SOFIA study groups

Kaplan-Meier (stair-step line) and estimated (smooth line) survival curves of patients treated with full-dose (solid line) or dose-adjusted (dashed line) sorafenib, according to BCLC stage: (A) entire population (BCLC B and C together); (B) BCLC B stage; (C) BCLC C stage.



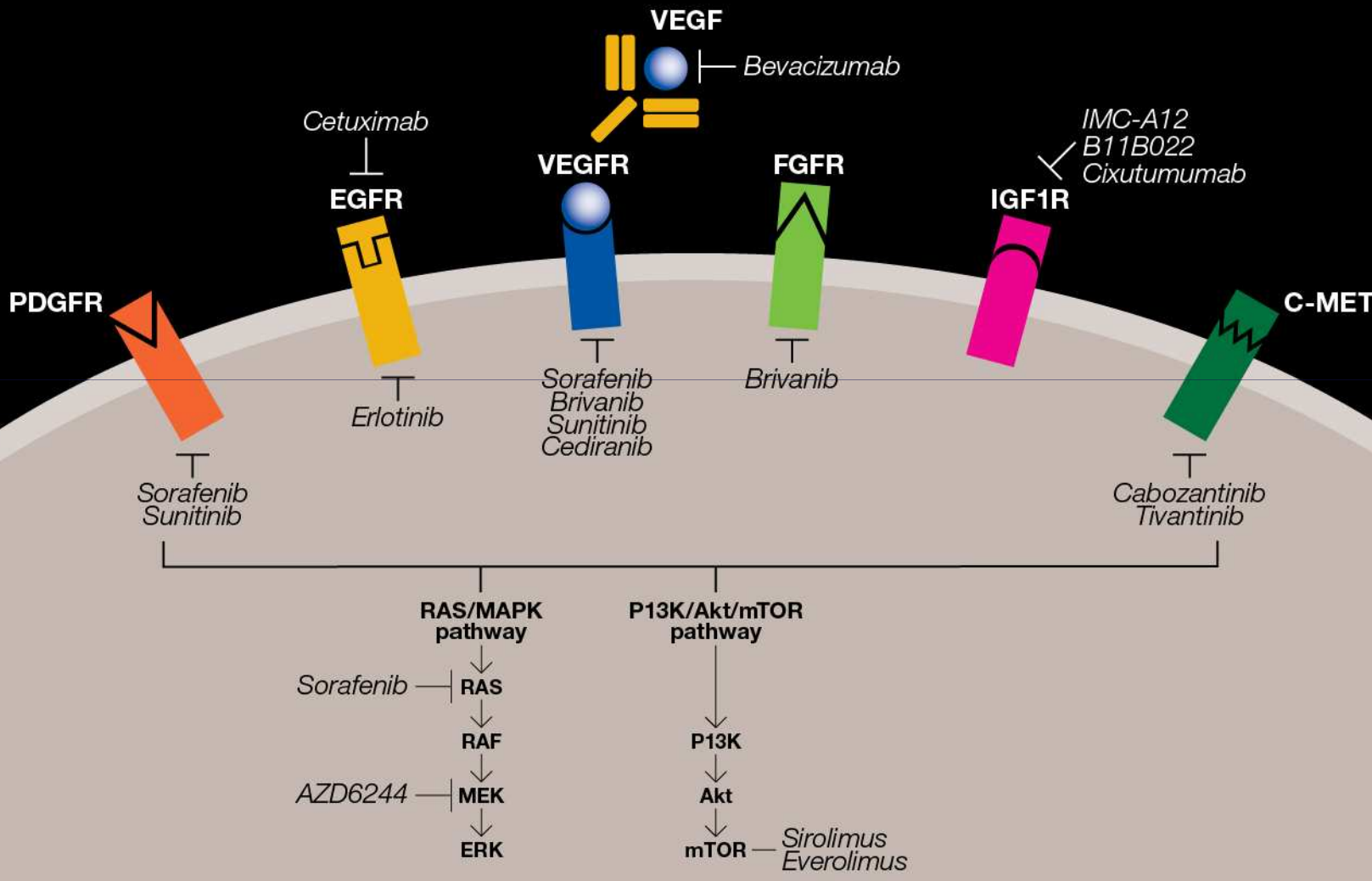
Camma C et al, Hepatology 2013

Cost-effectiveness of sorafenib for HCC

- Full-dose sorafenib was not cost-effective in the entire cohort of intermediate/advanced HCC patients.
- Dose-adjusted sorafenib is cost-effective in patients with advanced HCC but not in those with intermediate;
- Dose-adjusted sorafenib should be taken into account also in the adjuvant setting after resection/ablation or after TACE and for the design of future comparative trials versus novel targeted therapies.

Camma C et al, Hepatology 2013

Molecularly Targeted Therapy for HCC



Modified from Siegel et al, Hepatology 52:360-369, 2010

Phase III trials of second-line therapy in advanced HCC

Study	Phase	Experimental arm	Comparator arm	Patient population
NCT01035229 (EVOLVE-1)	III	Everolimus + BSC	Placebo + BSC	Pts who have progressed or are intolerant to sorafenib therapy, ECOG PS 0–2, Child-Pugh A
FAILED	III	Brivanib	Placebo	Pts who have failed ≥14 days of sorafenib, ECOG PS 0–2, Child-Pugh A-B7
NCT01108705 (BRISK-APS)	III	Brivanib + BSC	Placebo + BSC	Asian pts who have progressed or are intolerant to sorafenib therapy, ECOG PS 0–2, Child-Pugh A-B7
NCT01140347 (REACH)	III	Ramucirumab + BSC	Placebo + BSC	Pts who have progressed or are intolerant to sorafenib therapy, ECOG PS 0–1, Child-Pugh A
NCT01287585	III	ADI-PEG [ADI-PEG 20 (arginine deiminase formulated with polyethylene glycol)] + BSC	Placebo + BSC	Pts who have progressed or are intolerant to sorafenib therapy, ECOG PS 0–2, Child-Pugh A

www.clinicaltrials.gov

www.clinicaltrials.gov

Molecular Therapies (Including TKIs, mAbs, and Oligonucleotide Antisense) Currently Under Evaluation in HCC

	Drugs	Phases	Trials, n	Targets
1	Sorafenib	1, 1–2, 2, 3, 4	65	BRAF, VEGFR, PDGFR
2	Erlotinib	1, 1–2, 2, 3	13	EGFR
3	Everolimus	1, 1–2, 2, 3	7	MTORC1
4	Brivanib	1, 2, 3	6	FGFR, VEGFR, PDGFR
5	Sunitinib	2, 3	6	VEGFR, PDGFR, KIT
6	Rapamycin	1, 2–3, 3	5	MTORC1
7	Linifanib	2, 3	2	VEGF, PDGFR
8	PI-88	2, 3	2	Endo-β-D-glucuronidase heparinase
9	Ramucirumab	3	1	VEGFR2
10	Bevacizumab	1, 1–2, 2	20	VEGF
11	AZD6244	1–2, 2	4	MEK
12	Bortezomib	1, 2	4	Proteasome
13	TAC-101	1–2, 2	4	RAR-a
14	Cediranib	1, 2	3	VEGFR
15	Cetuximab	1, 2	3	EGFR
16	Cixutumumab	1, 2	3	IGF-1R
17	Temsirolimus	1, 2	3	MTORC1
18	ARQ197	1, 2	2	MET
19	BIBF1120	2	2	VEGFR, PDGFR, FGFR
20	Dasatinib	2	2	BCR-ABL
21	GC33	1	2	GPC3
22	Gefitinib	2	2	EGFR
23	Lapatinib	2	2	EGFR, HER2/neu
24	Licartin	2, 4	2	HAb18G/CD147
25	Pazopanib	2	2	VEGFR, PDGFR, KIT
26	Alvocidib	1, 2	2	Cyclin-dependent kinase
27	AEG35156	1–2	1	XIAP
28	AMG386	2	1	Angiopoietin
29	AVE1642	1, 2	1	IGF-1R
30	AZD8055	1–2	1	MTORC1, MTORC2
31	Regorafenib	2	1	VEGFR, TIE-2
32	BIIB022	1–2	1	IGF-1R
33	Belinostat	1–2	1	Histone deacetylase
34	CS-1008	2	1	TRAIL
35	CT-011	1–2	1	PD1
36	E7080	1–2	1	VEGFR, FGFR, SCFR
37	Foretinib	1	1	MET
38	IDN-6556	2	1	Caspase
39	IMC-1121B	2	1	VEGFR2
40	IMC-A12	2	1	IGF-1R
41	Ispinesib	2	1	Kinesin spindel protein
42	LBH589	1	1	Histone deacetylase
43	LY2181308	1–2	1	Survivin
44	Lonafarnib	2	1	Farnesyl-OH-transferase
45	MLN8237	2	1	Aurora kinase
46	Mapatumumab	1–2	1	TRAIL
47	OSI-906	2	1	IGF-1R, IR
48	Oblimersen	2	1	BCL2
49	Panobinostat	1	1	Histone deacetylase
50	Resminostat	2	1	Histone deacetylase
51	TSU-68	1–2	1	VEGFR, FGFR, PDGFR
52	Talabostat	1	1	Dipeptidyl peptidases
53	Tremelimumab	2	1	B7-CD28
54	Vandetanib	2	1	EGFR, VEGFR, RET
55	Vorinostat	1	1	Histone deacetylase
56	Z-208	1–2	1	RAR

NOTE. Data accessed on February 2011.
FGFR, fibroblast growth factor receptor; IGF-1R, insulin like growth factor receptor 1.

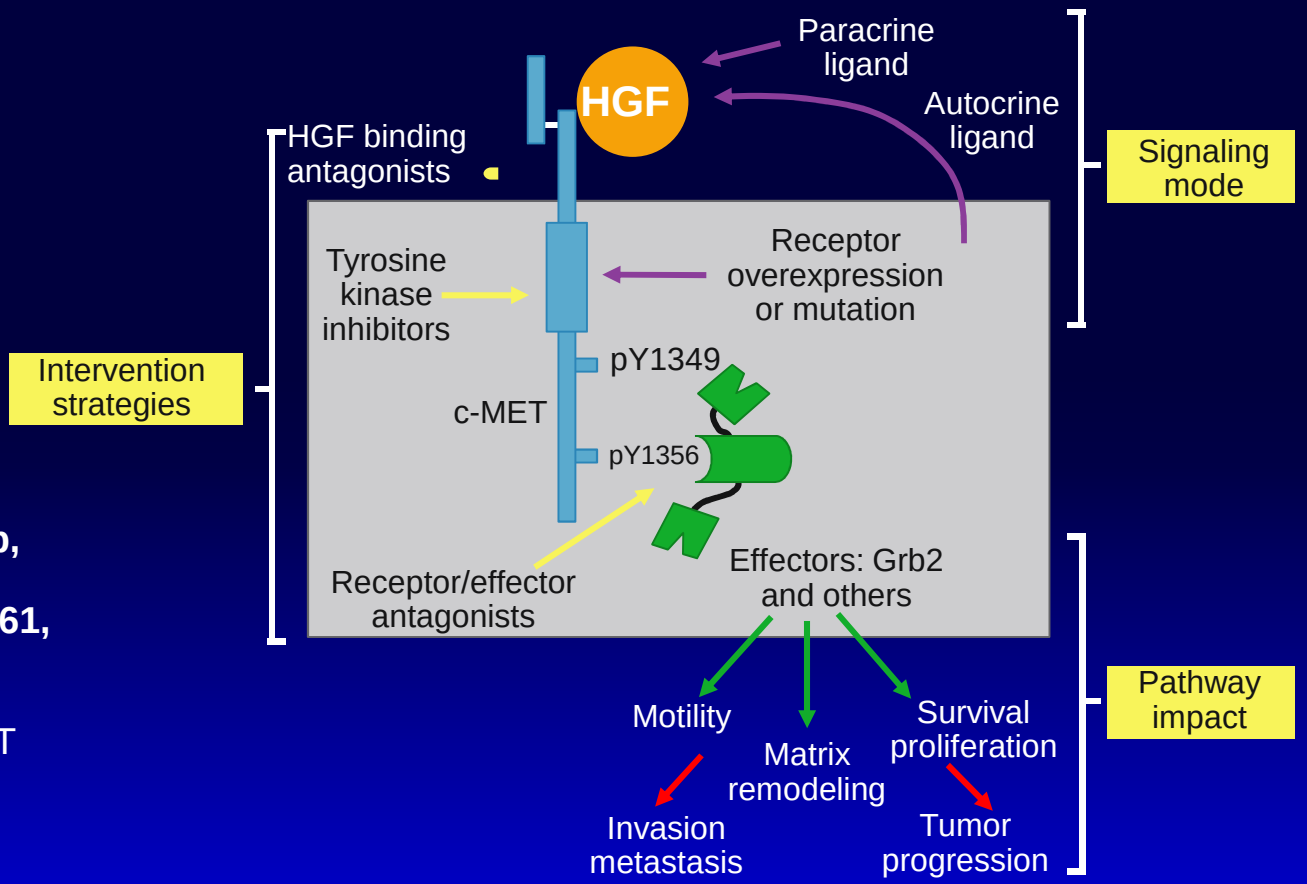
Villanueva and Llovet, 2011

The Role of MET in Oncogenesis

Rilotumumab: binds to HGF, blocks receptor binding

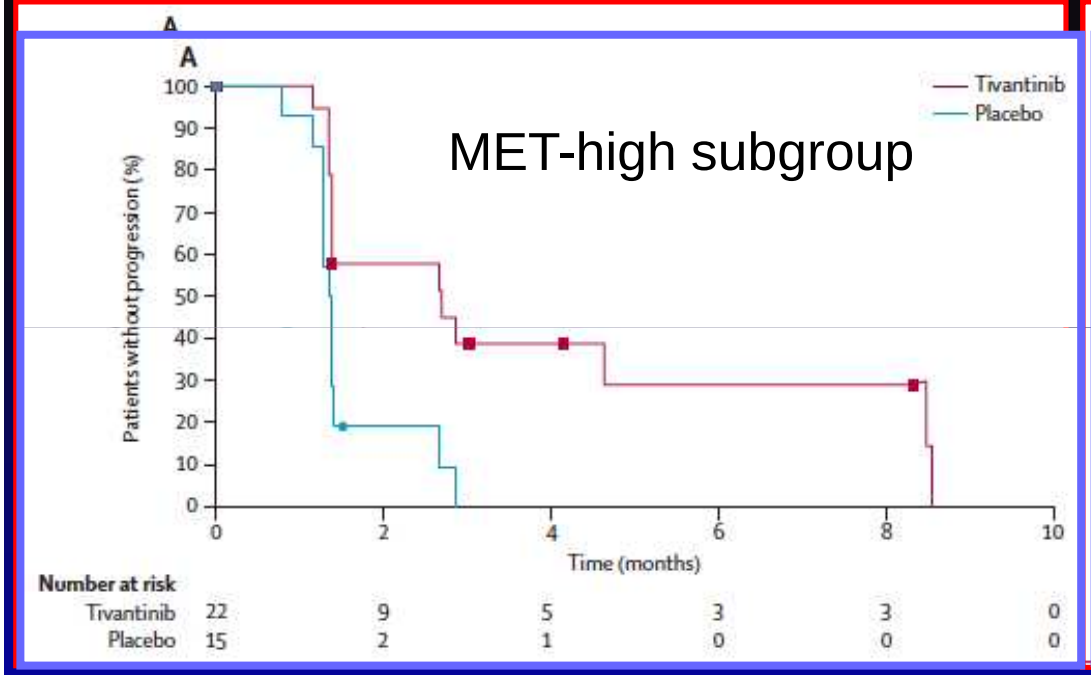
Onartuzumab (MetMAb): binds to MET, blocks HGF binding

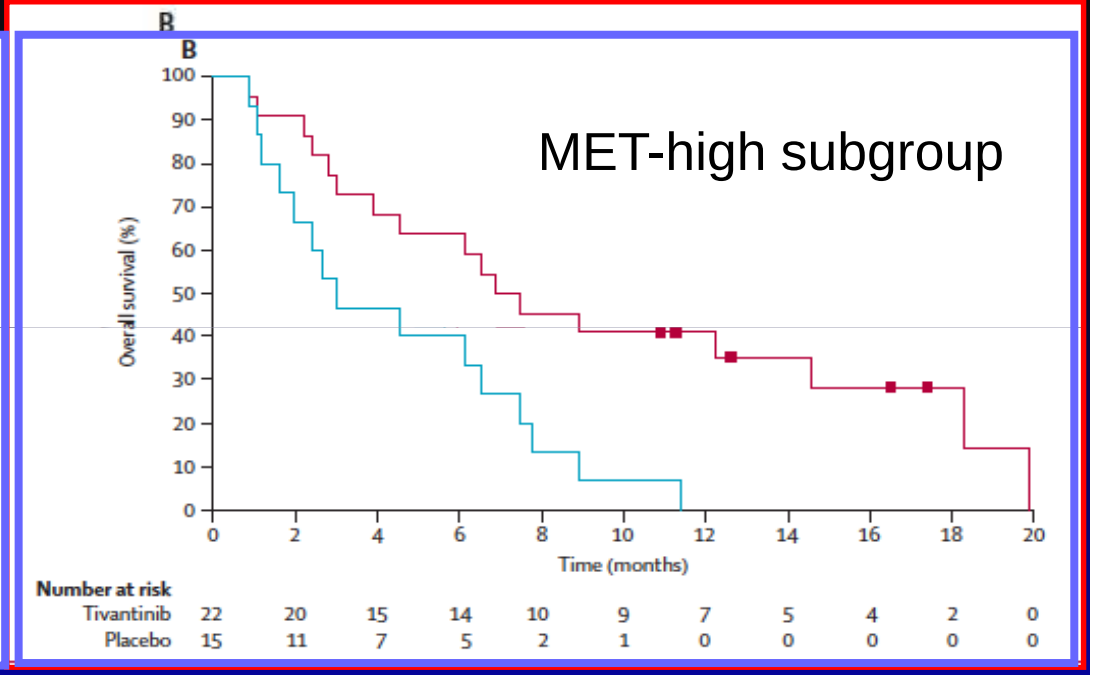
Cabozantinib, tivantinib, foretinib, crizotinib, JNJ38877605, MK2461, MP470, PF-04217903: small-molecule MET kinase inhibitors



Peruzzi B, et al. Clin Cancer Res. 2006;12:3657-3660.

Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study

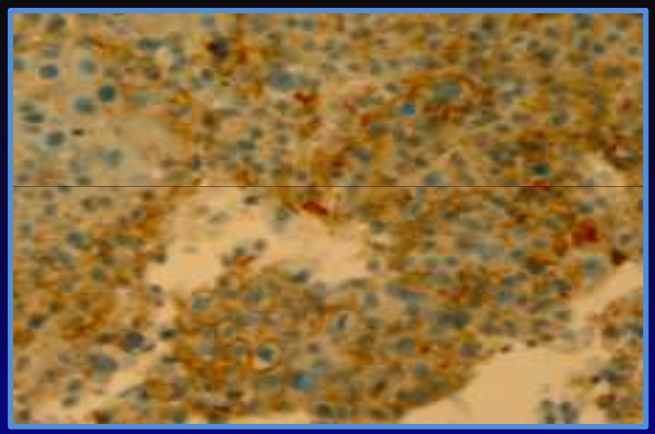




Santoro et al. , Lancet Oncology 2013

Liver histochemistry for c-met

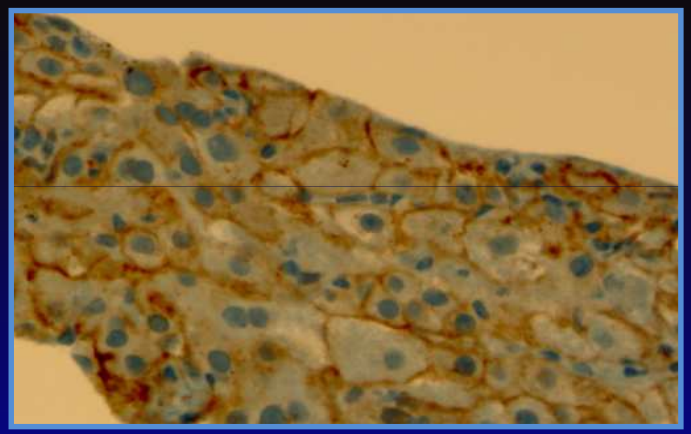
MET-High patient on Tivantinib



OS 16.49 mos

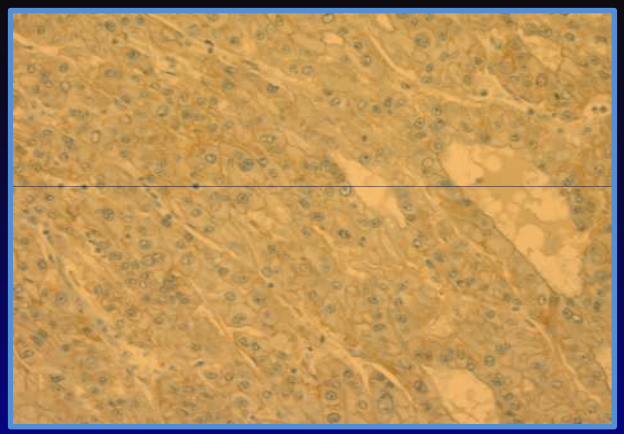
(censored = pt still alive as of April 2012)

MET-High patient on Placebo



OS 2.69 mos

MET-Low patient on Placebo



OS 9 mos

Courtesy of G. Abbadessa, Arqule
Santoro et al. Lancet Oncology 2013

Conclusions

1. HCC is a inflammatory tumor with an extremely heterogeneous molecular background

2. Inhibition of single pathways is associated with a positive therapeutic result only in case of strong hyper-expression of that pathway

3. Molecular characteristics are dynamic and can change during course of disease

1. This means that the targeted therapeutic approach has to be complex and adapted to changing conditions of the tumoral micro-environment.

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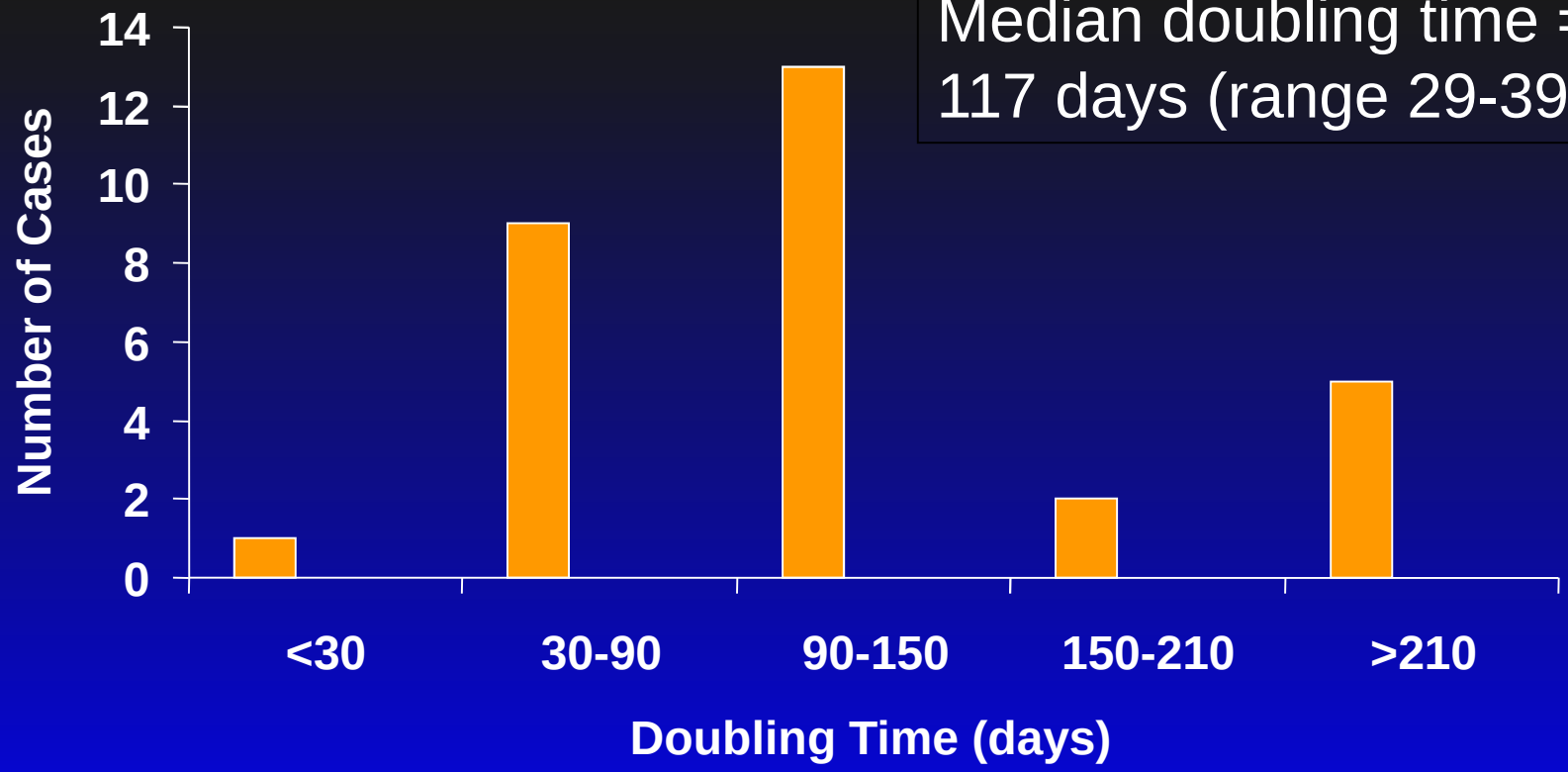
Luisa Losi

Liver Transplant, Modena

Giorgio Gerunda Gian Piero Guerrini

Growth Rate of HCC

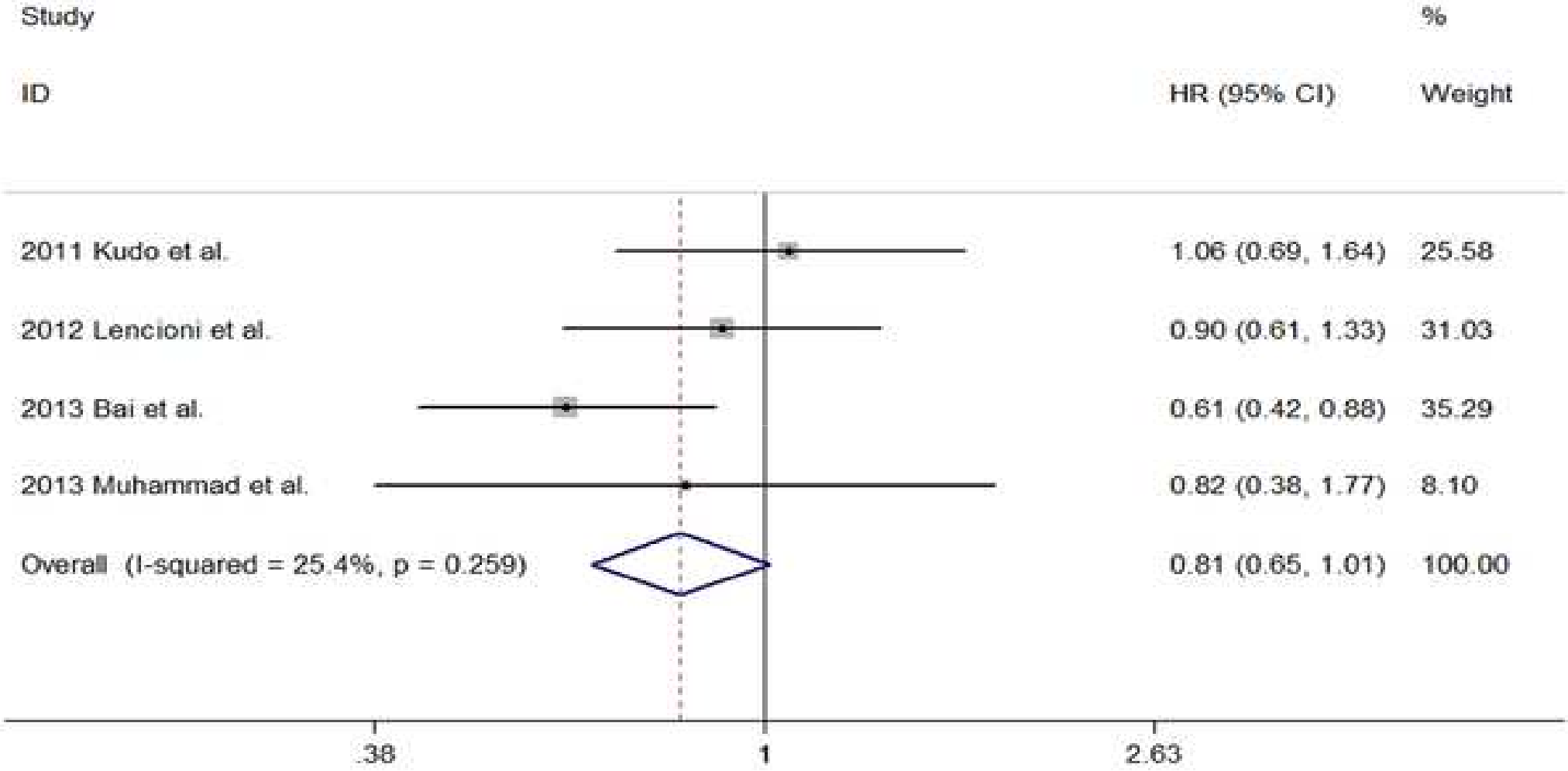


Sheu J-C et al, Gastro 1985;89:259

Advanced Disease:
Chemotherapy Historically Disappointing

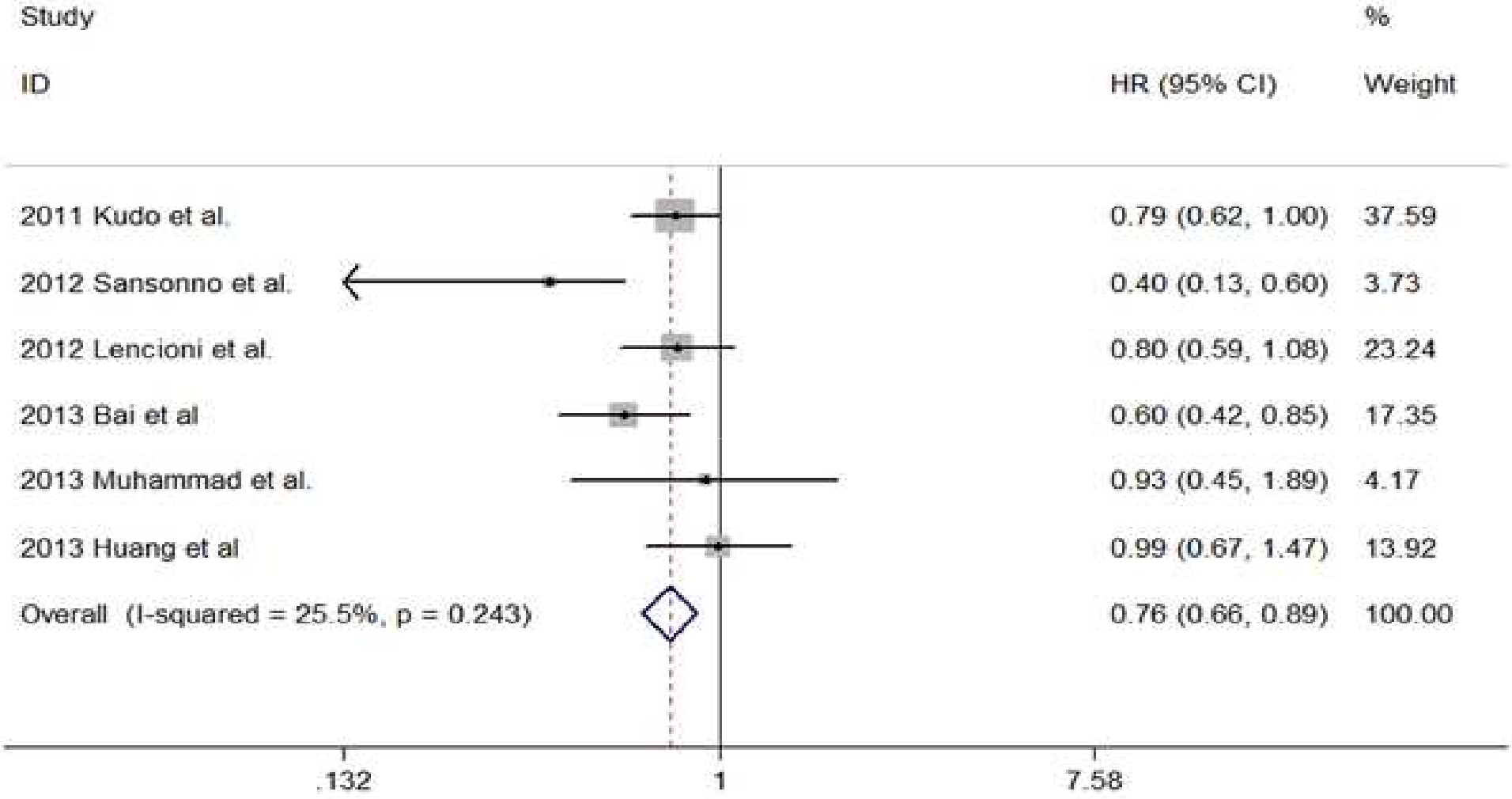
- Difficult to give chemotherapy with liver compromise
- Overexpression of MDR-1 gene
- Targets until now have been poorly defined

Forest plot showing the associations of the overall survival (OS) between TACE alone group and sorafenib combined with TACE group for patients with unresctable HCC.



Liu L, Chen H, Wang M, Zhao Y, et al. (2014) Combination Therapy of Sorafenib and TACE for Unresectable HCC: A Systematic Review and Meta-Analysis. PLoS ONE 9(3): e91124. doi:10.1371/journal.pone.0091124
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0091124

Forest plot showing the associations of the time to progression (TTP) between TACE alone group and sorafenib combined with TACE group for patients with unresctable HCC.



Liu L, Chen H, Wang M, Zhao Y, et al. (2014) Combination Therapy of Sorafenib and TACE for Unresectable HCC: A Systematic Review and Meta-Analysis. PLoS ONE 9(3): e91124. doi:10.1371/journal.pone.0091124
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0091124

Intra-arterial Radioembolization With Yttrium-90: Rationale and History

- Radioembolization: Use of intra-arterially delivered yttrium-90 microspheres emitting high-dose radiation for the treatment of liver tumors
- Yttrium-90 microspheres
  - Average diameter: 20-30 μm
  - 100% pure beta emitter (0.9367 MeV)
  - Physical half-life: 64.2 hours
  - Irradiates tissue with average path length of 2.5 mm (maximum: 11 mm)

Murthy R, et al. Biomed Imaging Interv J. 2006;3:e43.

Clinical Response to Yttrium-90 Microspheres

Outcome	Dancey et al[1] (N = 20)	Carr et al[2] (N = 65)	Geschwind et al[3] (N = 80)	Salem et al[4] (N = 43)
Response rate, %		39		47
	y (> 104 Gy)			
▪ Okuda stage I		649 days	628 days	24.4 mos
▪ Okuda stage II		302 days	384 days	12.5 mos

1. Dancey JE, et al. J Nucl Med. 2000;41:1673-1681.
2. Carr BI. Liver Transpl. 2004;10(2 suppl 1):S107-S110.
3. Geschwind JF, et al. Gastroenterology. 2004;127(5 suppl 1):S194-S205.
4. Salem R, et al. J Vasc Interv Radiol. 2005;16:1627-1639.