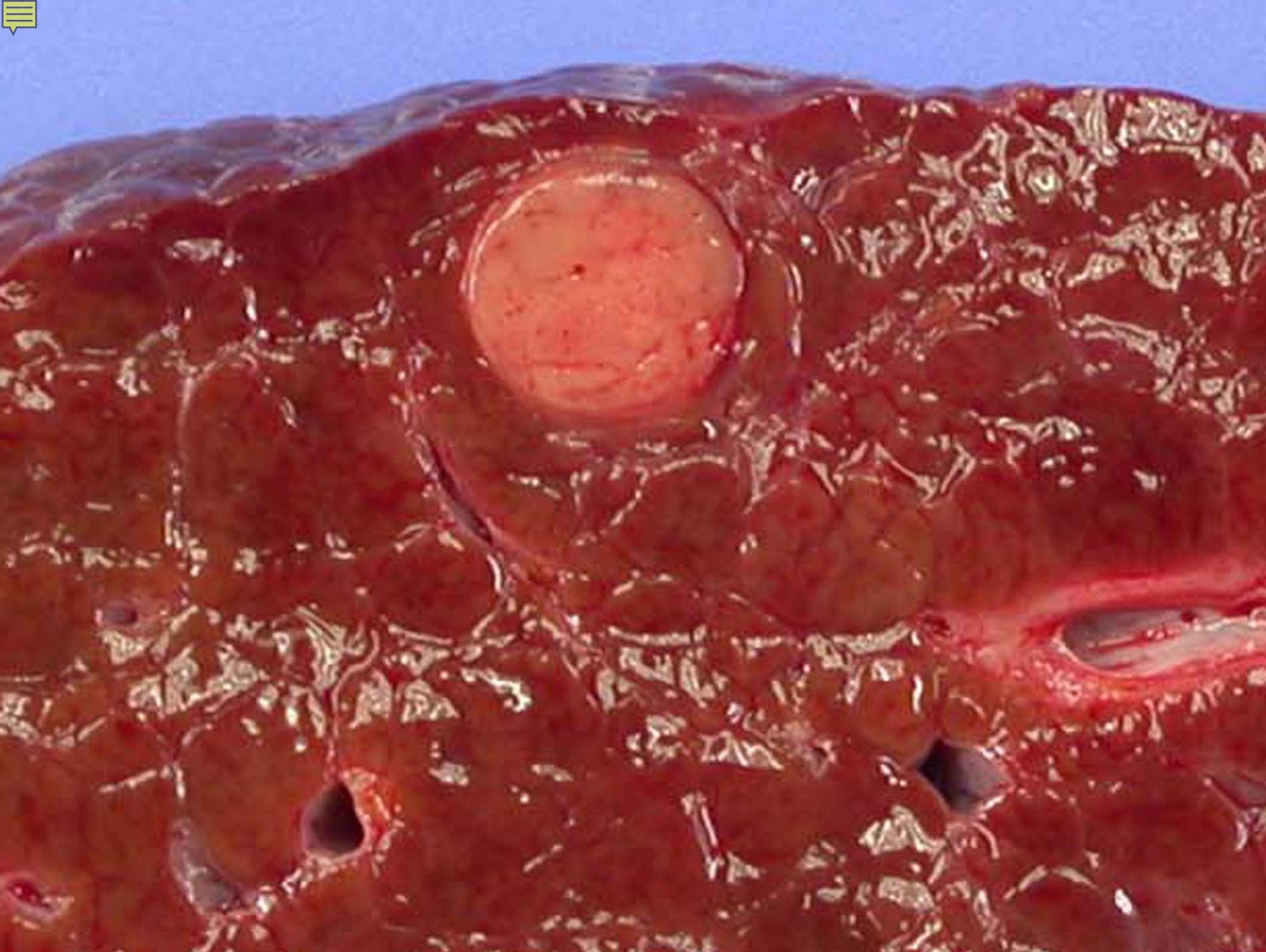
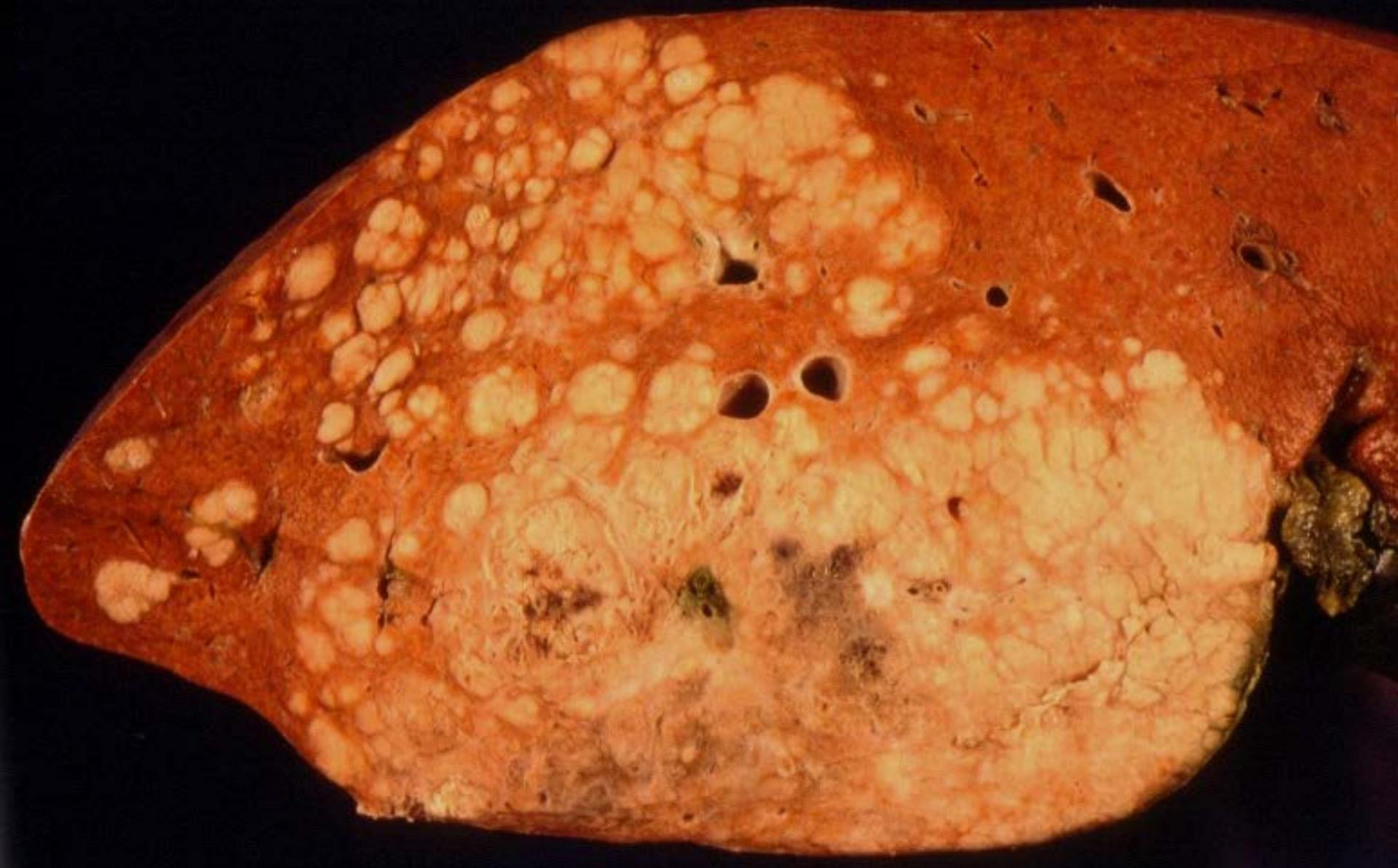


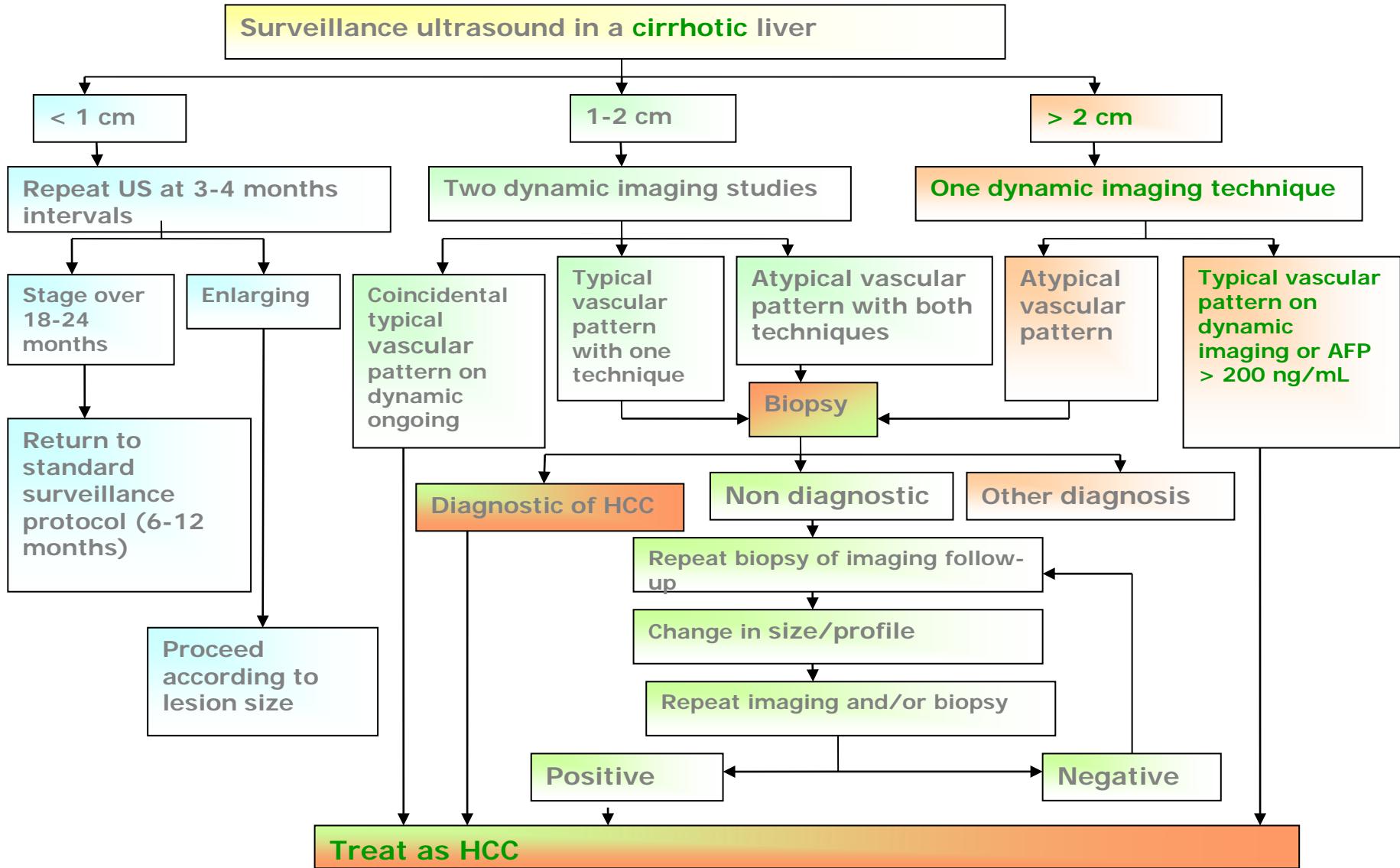
Μη χειρουργική αντιμετώπιση του ηπατοκυτταρικού καρκίνου

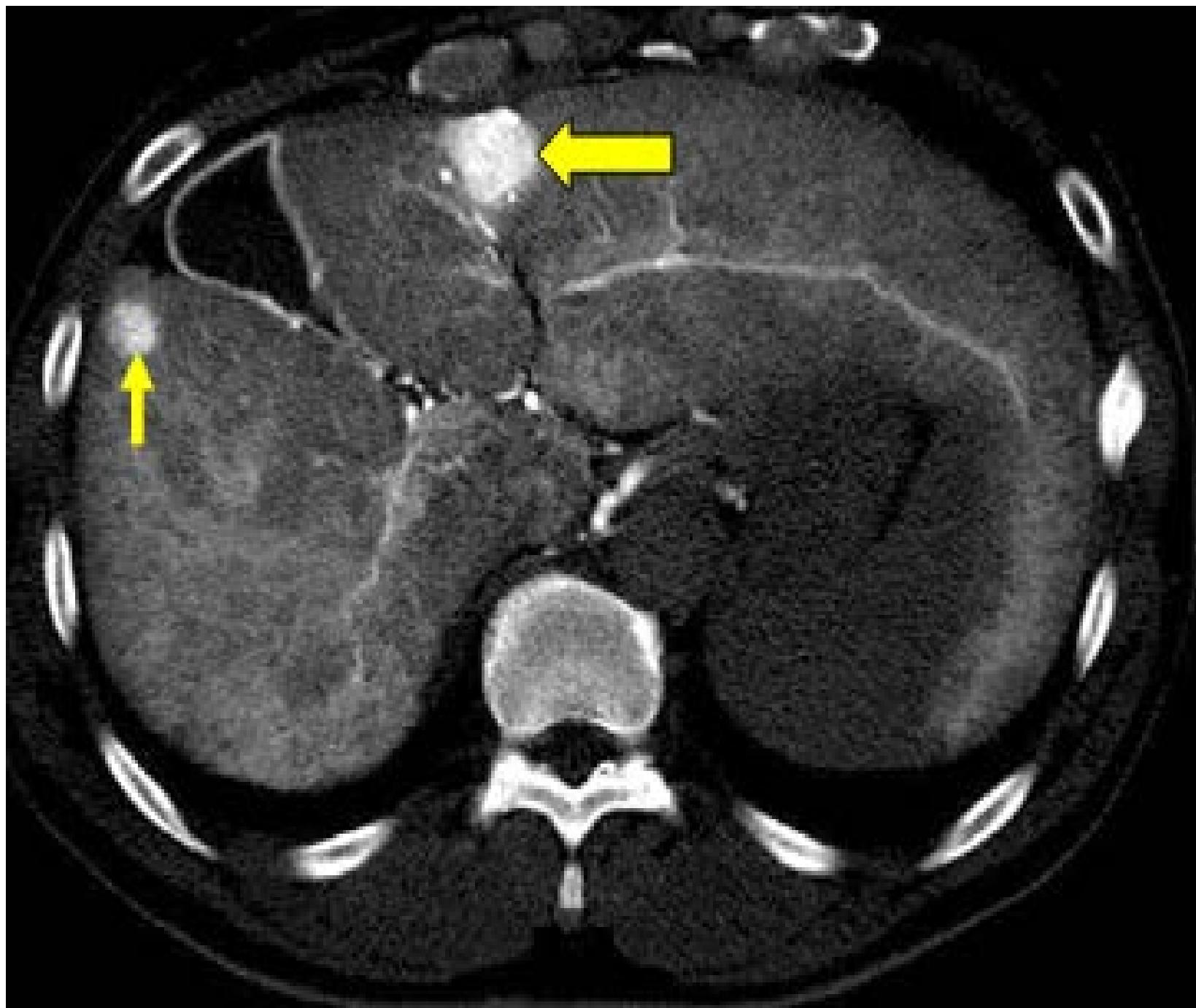
Γεώργιος Γερμανίδης,
Α΄ Παθολογική Κλινική Α.Π.Θ.,
Π.Γ.Ν.Θ Α.Χ.Ε.Π.Α



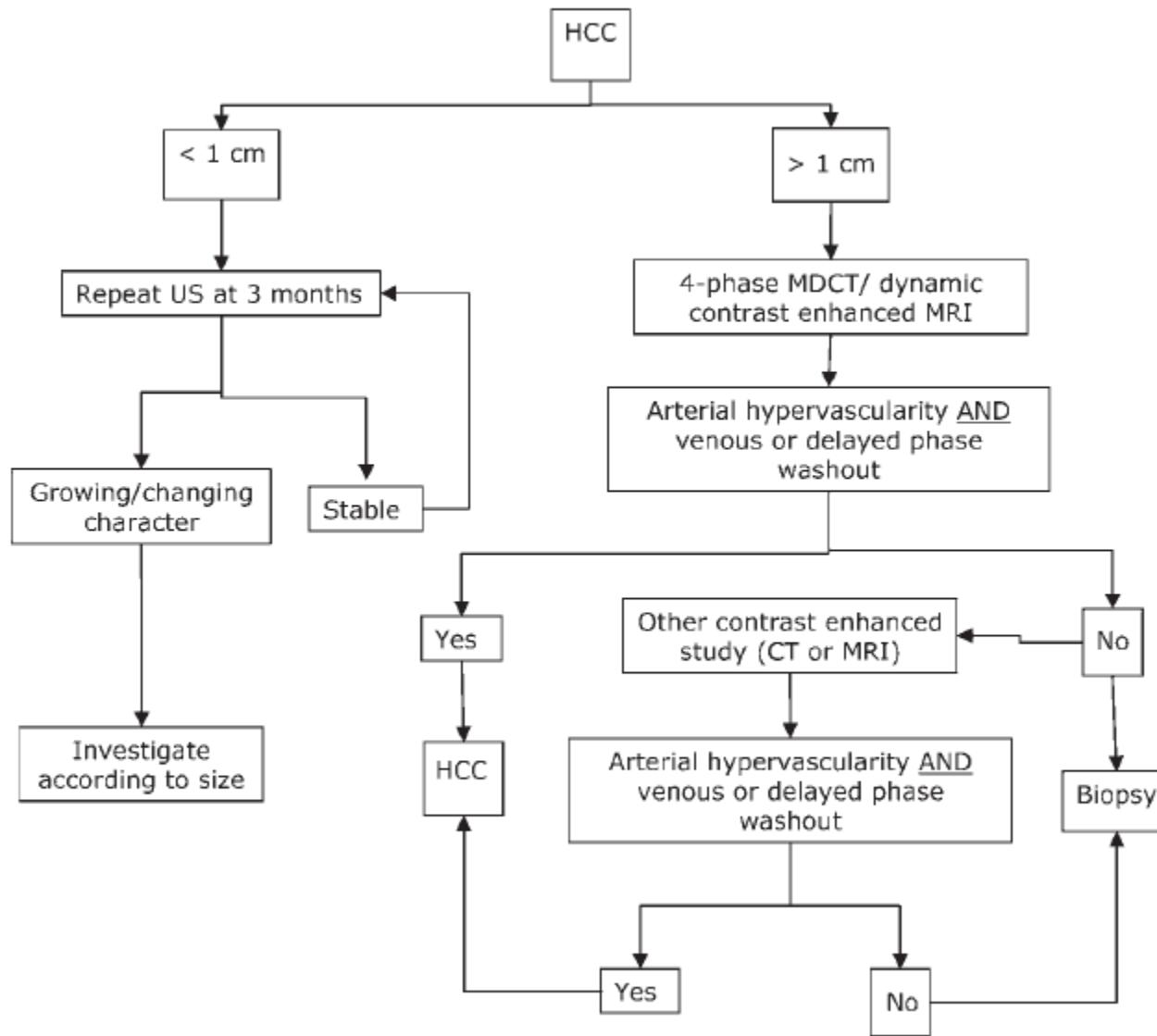


AASLD Criteria for HCC





Investigation of nodules found on screening in patients at risk for HCC (new AASLD Criteria-2010)



US-βιοψία μικρού ηπατικού οζιδίου που εμφανίζεται σε παρακολούθηση ασθενών με κίρρωση

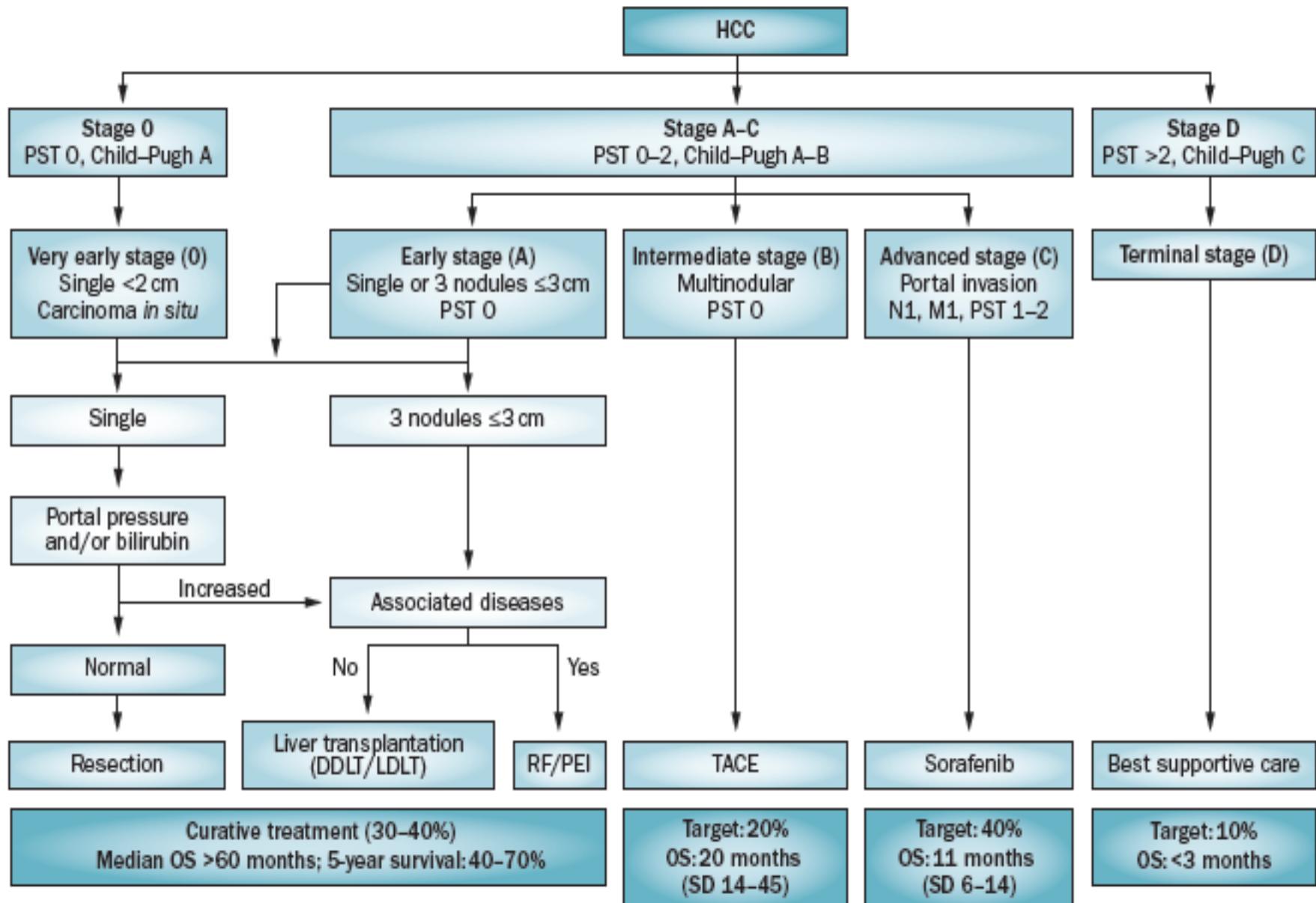
- **4375 ασθενείς με κίρρωση-επιτήρηση με US**
- **294 οζίδια <20mm (48 <10mm)**
- **258/294 (87,6%) των οζιδίων αποδείχθηκαν ΗΚΚ**
- **33/48 (68,7%) των <10mm**
- **Η διαγνωστική ακρίβεια για US-βιοψία ήταν 89,4% συνολικά (88,6% για οζίδια <10mm)**

HGDN και μικρού μεγέθους ΗΚΚ (2-3cm) με καλή διαφοροποίηση

- Δύσκολη διάγνωση ακτινολογικά, απαραίτητη η βιοψία
- Περιπτώσεις αμφίβολες με μικρού μεγέθους βιοψίες και χρώση H&E
- **Έρευνα για γενετικά «αποτυπώματα» ή «υπογραφές» του HGDN vs πρώιμου ΗΚΚ**
- Στην πράξη, ρεαλιστικά, χρήση ανοσοϊστοχημείας σε βιοψίες για ανίχνευση
 - glypican 3 (GPC3) – sens.77%, sp.96%
 - glutamine synthase
 - HSP 70
 - CD31, CD34, BNH9 σε δυσπλαστικά οζίδια και ΗΚΚ

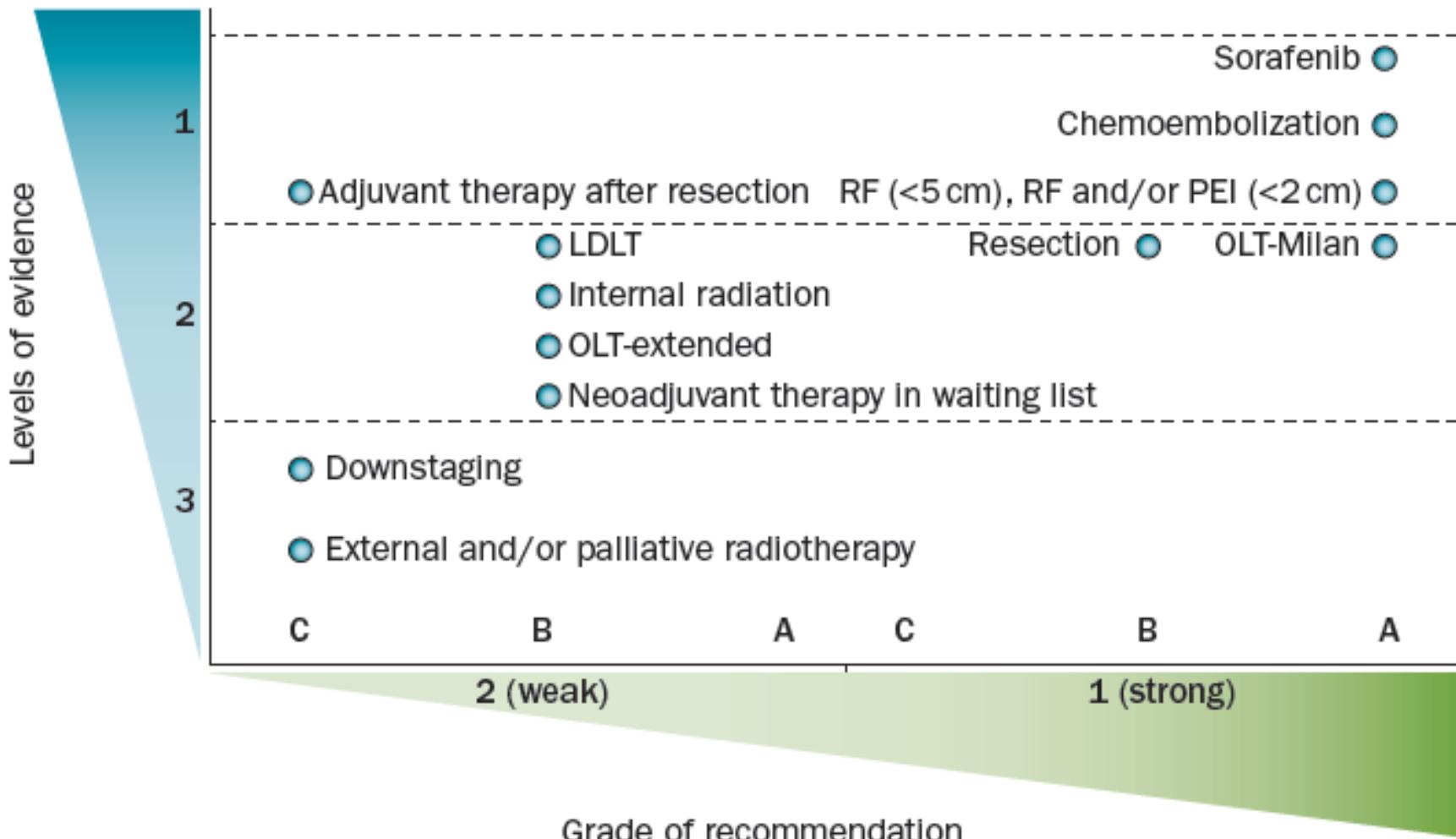
HCC THERAPEUTIC STRATEGY-EASL-EORTC 2012

J. Hepatol. 56, 908-943 (2012)



Therapeutic interventions in HCC according to level of evidence and grade of recommendation

J. Hepatol. 56, 908-943 (2012)



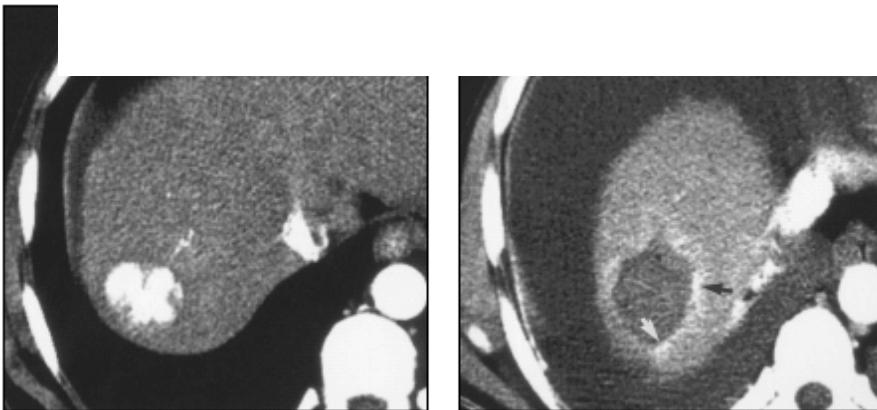
- Deviations from current guidelines are very frequent in clinical practice!

Table 1 | Milestones in HCC research reported during the past 30 years*

Citations	Reference	Title	Thematic area	Direct influence on CPG	Citations per year
Treatment					
2,331	Mazzaferro et al. (1996) ¹²	Liver transplantation for the treatment of small HCC in patients with cirrhosis	Surgery	Yes	129
1,777	Llovet et al. (2008) ⁷	Sorafenib in advanced HCC	Systemic therapy	Yes	325
984	Llovet et al. (2002) ⁹⁶	Arterial embolization or chemoembolization vs symptomatic treatment in patients with unresectable HCC: a randomized controlled trial	Locoregional	Yes	84
831	Llovet et al. (2003) ¹¹	Systematic review of randomized trials for unresectable HCC: chemoembolization improves survival	Locoregional	Yes	78
791	Livraghi et al. (1999) ⁹⁷	Small HCC: treatment with radiofrequency ablation vs ethanol injection	Locoregional	Yes	56
791	Lo et al. (2002) ⁹⁸	Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable HCC	Locoregional	Yes	59
722	Llovet et al. (1999) ⁹⁹	Intention-to-treat analysis of surgical treatment for early HCC: resection vs transplantation	Surgery	Yes	50
730	Curley et al. (1999) ¹⁰⁰	Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients	Locoregional	No	49
663	Livraghi et al. (1995) ¹⁰¹	HCC and cirrhosis in 146 patients: long-term results of percutaneous ethanol injection	Locoregional	Yes	36

Radiofrequency Ablation of the Liver: Current Status

John P. McGahan¹ and Gerald D. Dodd III²



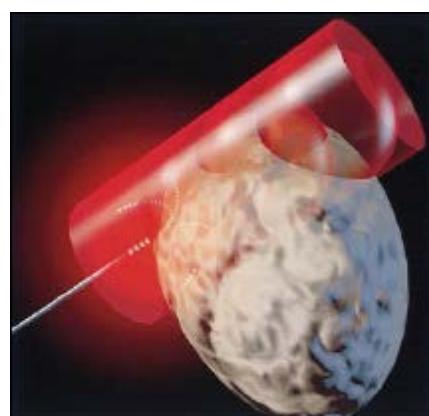
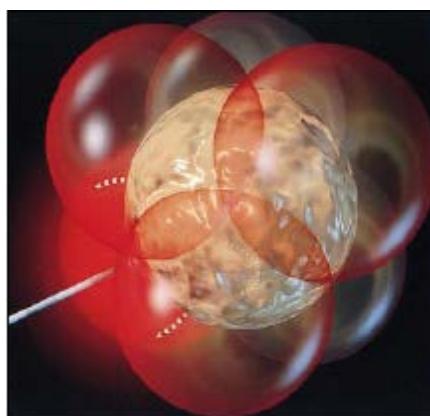
AJR:176, January 2001

Arch Surg. 2006;141:181-0

Table 1. Included HCC Comparative Studies (13 Studies)

Source	Sample Size (Comparison)	Level of Evidence
Kurokohchi et al, ¹⁵ 2002	39 (20 RFA, 19 RFA-PEI)	II
Lencioni et al, ¹⁶ 2003, includes Olschewski et al, ²⁸ 2001	102 (52 RFA, 50 PEI)	II
Shibata et al, ¹⁷ 2002	72 (36 RFA, 36 MCT)	II
Shiina et al, ¹⁸ 2000	60 (31 RFA, 29 PEI)	II
Livraghi et al, ¹⁹ 1999, includes Livraghi et al, ²⁹ 1998	86 (42 RFA, 44 PEI)	III-1
Gasparini et al, ²⁰ 2001	34 (10 RFA, 24 RFA-TACE)	III-2
Ikeda et al, ²¹ 2001	119 (23 RFA, 96 PEI)	III-2
Catalano et al, ²² 2000, includes Catalano et al, ³⁰ 1999	102 (32 RFA, 56 multiple-session PEI, 14 single-session PEI, 14 LITT)	III-3
Catalano et al, ²³ 2001	61 (16 RFA, 40 multiple-session PEI, 5 single-session PEI, 6 LITT)	III-3
Izumi et al, ²⁴ 2001	84 (16 RFA, 68 MCT)	III-3
Kouyama et al, ²⁵ 2000	40 (20 RFA, 20 MCT)	III-3
Livraghi et al, ²⁶ 2001	20 (10 RFA, 10 TACE)	III-3
Yu et al, ²⁷ 2002	145 (57 RFA, 88 surgical resection)	III-3

Abbreviations: HCC, hepatocellular carcinoma; LITT, laser-induced thermotherapy; MCT, microwave coagulation therapy; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.



Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma

An Analysis of 1000 Cases

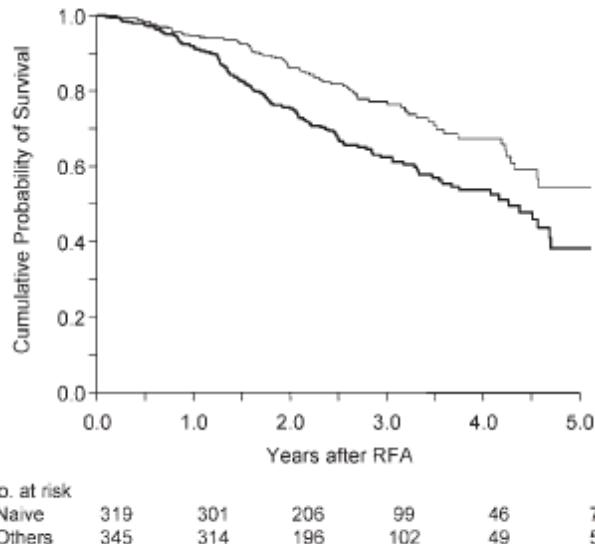
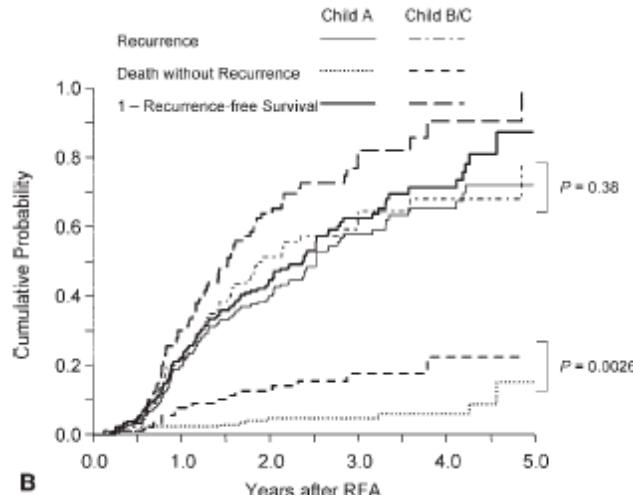


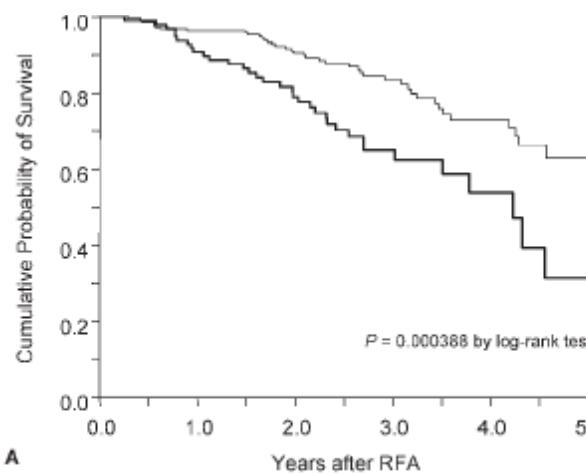
FIGURE 1. The cumulative survival rates of naive (thin line) and nonnaive (thick line) patients who received radiofrequency ablation (RFA). The cumulative survival rates estimated by the Kaplan-Meier method at 1, 2, 3, 4, and 5 years were 94.7%, 86.1%, 77.7%, 67.4%, and 54.3% for naive patients and 91.8%, 75.6%, 62.4%, 53.7%, and 38.2% for nonnaive patients, respectively.

Ryosuke Tateishi, M.D.
Shuichiro Shilina, M.D.
Takuma Teratani, M.D.
Shuntaro Obi, M.D.
Shinpel Sato, M.D.
Yukihiro Kolke, M.D., Ph.D.
Tomonori Fujishima, M.D.
Haruhiko Yoshida, M.D., Ph.D.
Takao Kawabe, M.D., Ph.D.
Masao Omata, M.D., Ph.D.

Department of Gastroenterology, University of Tokyo, Tokyo, Japan.



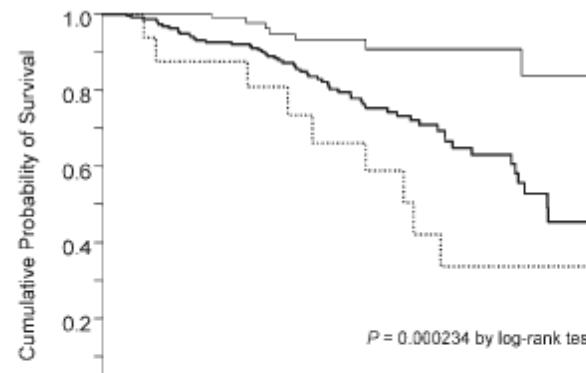
1202 CANCER March 15, 2005 / Volume 103 / Number 6



No. at risk	Child A	Child B/C
Child A	221	213
Child B/C	98	88



No. at risk	Child A	Child B/C
Child A	221	213
Child B/C	98	88



No. at risk	<2cm	2.1-5cm	>5cm
<2cm	87	87	58
2.1-5cm	215	200	145
>5cm	17	14	10

A Randomized Controlled Trial of Radiofrequency Ablation With Ethanol Injection for Small Hepatocellular Carcinoma

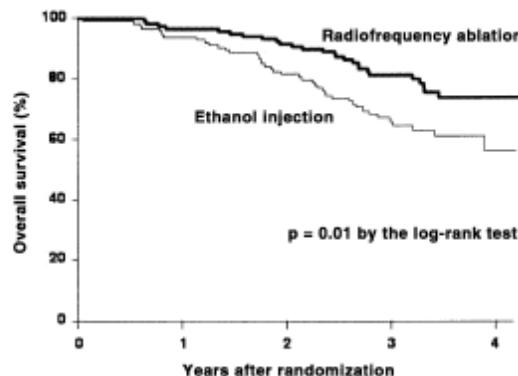


Figure 2. Survival in the 232 eligible patients, according to the treatment group. The actuarial 4-year survival rate was 74% in the radiofrequency-ablation group, whereas it was 57% in the ethanol-injection group.

TABLE 2
Major Complications after RFA

Complications	No. of complications	Prevalence (%)	
		Per treatment	Per session
Immediate (within 24 hrs)			
Intrapertitoneal hemorrhage requiring blood transfusion	4	0.4	0.19
Pleural effusion requiring drainage	4	0.4	0.19
Hepatic infarction	2	0.2	0.096
Pneumothorax requiring drainage	1	0.1	0.048
Hemothorax requiring drainage	1	0.1	0.048
Bile peritonitis	1	0.1	0.048
Periprocedural (within 30 days)			
Hepatic abscess requiring drainage	7	0.7	0.34
Bronchobiliary fistula	2	0.2	0.096
Duodenal perforation	1	0.1	0.048
Colonic penetration	1	0.1	0.048
Gastric penetration	1	0.1	0.048
Delayed			
Neoplastic seeding	15	1.5	0.72
Total	40	4.0	1.9

Figure 4. Local tumor progression in the 232 eligible patients according to the treatment group. The actuarial 4-year rate of progression was 1.7% in the radiofrequency-ablation group, whereas it was 11% in the ethanol-injection group.

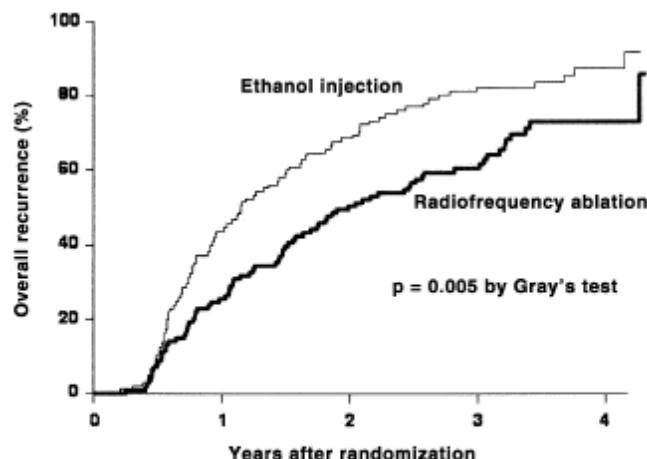


Figure 3. Overall recurrence in the 232 eligible patients, according to the treatment group. The estimated 4-year rate of overall recurrence was 70% in the radiofrequency-ablation group, whereas it was 85% in the ethanol-injection group.

TABLE 3
Minor Complications after RFA

Complications	No. of complications	Prevalence (%)	
		Per treatment	Per session
Immediate (within 24 hrs)			
Self-limiting hemobilia	3	0.3	0.14
Skin burn (entrance point)	3	0.3	0.14
Periprocedural (within 30 days)			
Self-limiting portal vein thrombosis	4	0.4	0.19
Delayed			
Biloma	7	0.7	0.34
Total	17	1.7	0.82

Studies describing 3–5-year survival rates of patients with single HCC <2cm treated by percutaneous ablation

Journal of Hepatology 2012 | S75–S87

Table 2. Studies describing 3–5-year survival rates of patients with single HCC <2 cm treated by percutaneous ablation.

Author, year [Ref.]	n (Child-Pugh A/B/C)	Treatment	3-year survival (%)	5-year survival (%)	Major complications (%)	Recurrence (%)
Arii, 2000 [52]*	767 (767/0/0)	PEI	81.4	54.2	-	-
Omata, 2004 [56]	92 (NA)	PEI	-	74	-	-
Sala, 2004 [57]	34 (34/0/0)	PEI/RFA	72	63	-	-
Tateishi, 2005 [59]	87 (NA)	RFA	90.8	83.8	-	-
Shiina, 2005 [58]	118 (85/33/0) (72 single <3 cm) (45 <2 cm)	RFA	- 86	74** 77**	5.1	70 (4 yr)
	114 (85/29/0) (60 single <3 cm) (57 <2 cm)	PEI	- 73	57** 64**	2.6	85 (4 yr)
Lin, 2005 [54]	62 (46/16/0) 36 <2 cm (NA)	RFA	74 (75 <2 cm)	-	4.8	-
	62 (37/25/0) 37 <2 cm (NA)	PEI	51 (67 <2 cm)	-	0	-
	63 (38/25/0) 38 <2 cm (NA)	PAI	53 (69 <2 cm)	-	0	-
Choi, 2007 [53]	226 (NA)	RFA	77.3	65.6	-	-
Livragli, 2008 [55]***	218 (218/0/0) 100 (potentially resectable)	RFA	76 89	55 68	1.8	80 (5 yr)

An overview of evidence-based management of hepatocellular carcinoma: a meta-analysis.

Salhab M, Canelo R. *J Cancer Res Ther.* 2011 Oct-Dec;7(4):463-75.

- The meta-analysis comparing PEI to radiofrequency ablation (RFA) showed *RFA to be superior to PEI* in terms of overall survival at three years (odds ratio 1.698; 95% CI 1.206 - 2.391; P = 0.002).
- When *adverse events* were considered there was *no statistically significant difference* between the RFA and PEI groups (odds ratio 1.199; 95% CI 0.571- 2.521; P = 0.632).
- **RFA should be the first-line treatment in patients with a single small HCC tumor ≤ 3 cm.**

TACE



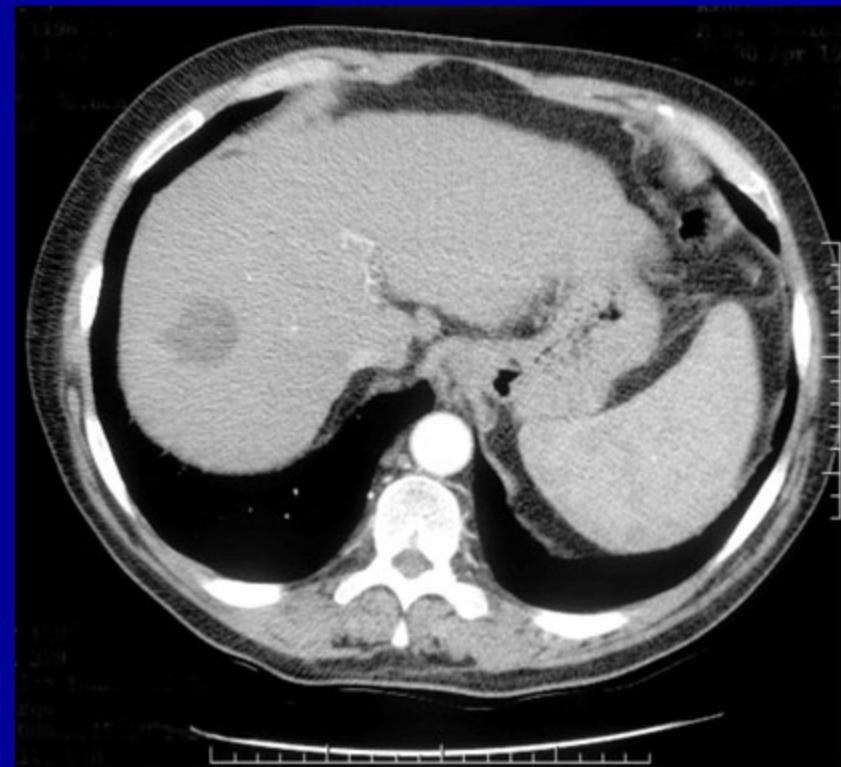
OPTIMAL SELECTION CRITERIA FOR TRANSARTERIAL THERAPY

- **Inclusion**
 - Unresectable
 - >3cm or >3 lesions
 - Child Pugh A and B
 - Okuda I or II
 - Good performance status (PS)
- **Exclusion**
 - Vascular invasion
 - Refractory Ascites
 - Renal impairment
 - Poor PS
 - Encephalopathy
 - Extrahepatic disease
 - Okuda III

ASSESSMENT OF TUMOUR RESPONSE TO TACE



pre treatment
AFP 1824



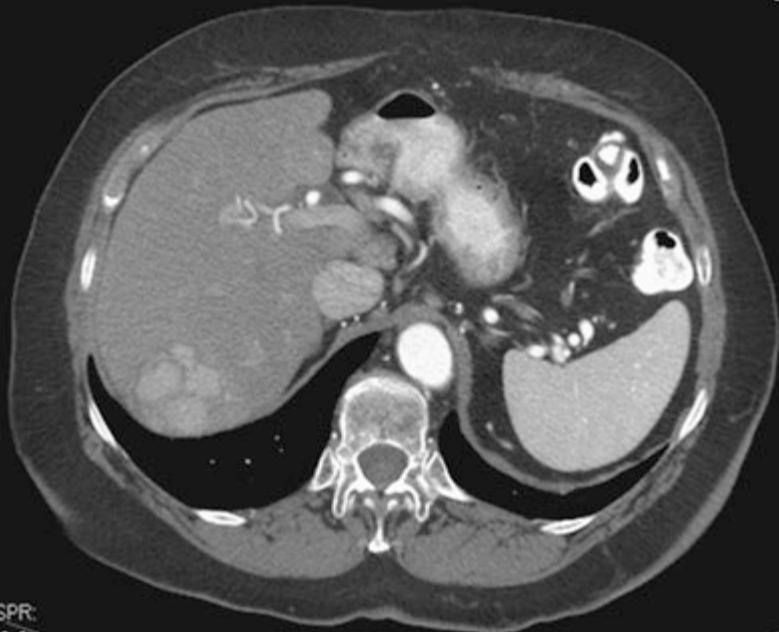
post treatment
AFP 99

Stable disease by RECIST Complete response by EASL criteria

IM:32 of 87

307.5

(a)



RT: SPR:

V: 440.0 mm-mm

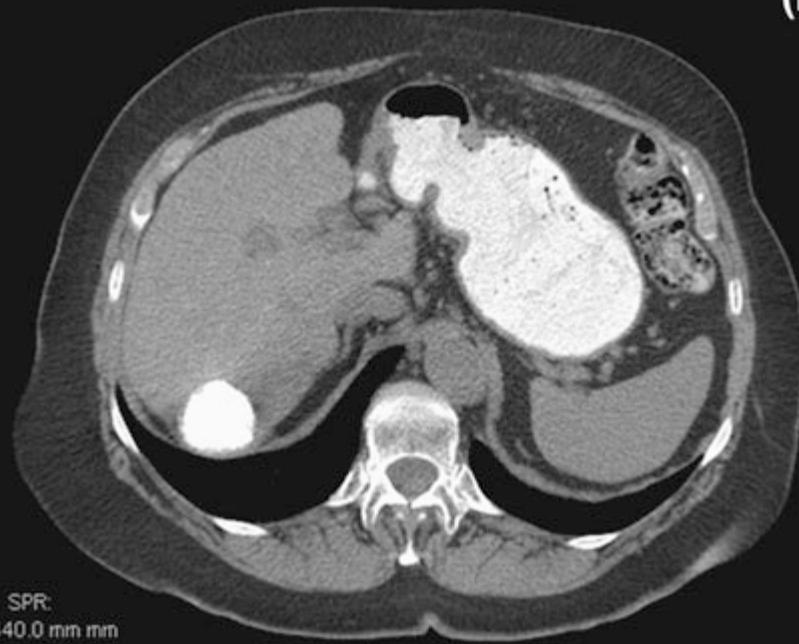
kVp - 346 mA

50 mm

Revolution time: 0.8000000119209

264.5

(b)



RT: SPR:

V: 440.0 mm-mm

kVp - 248 mA

50 mm

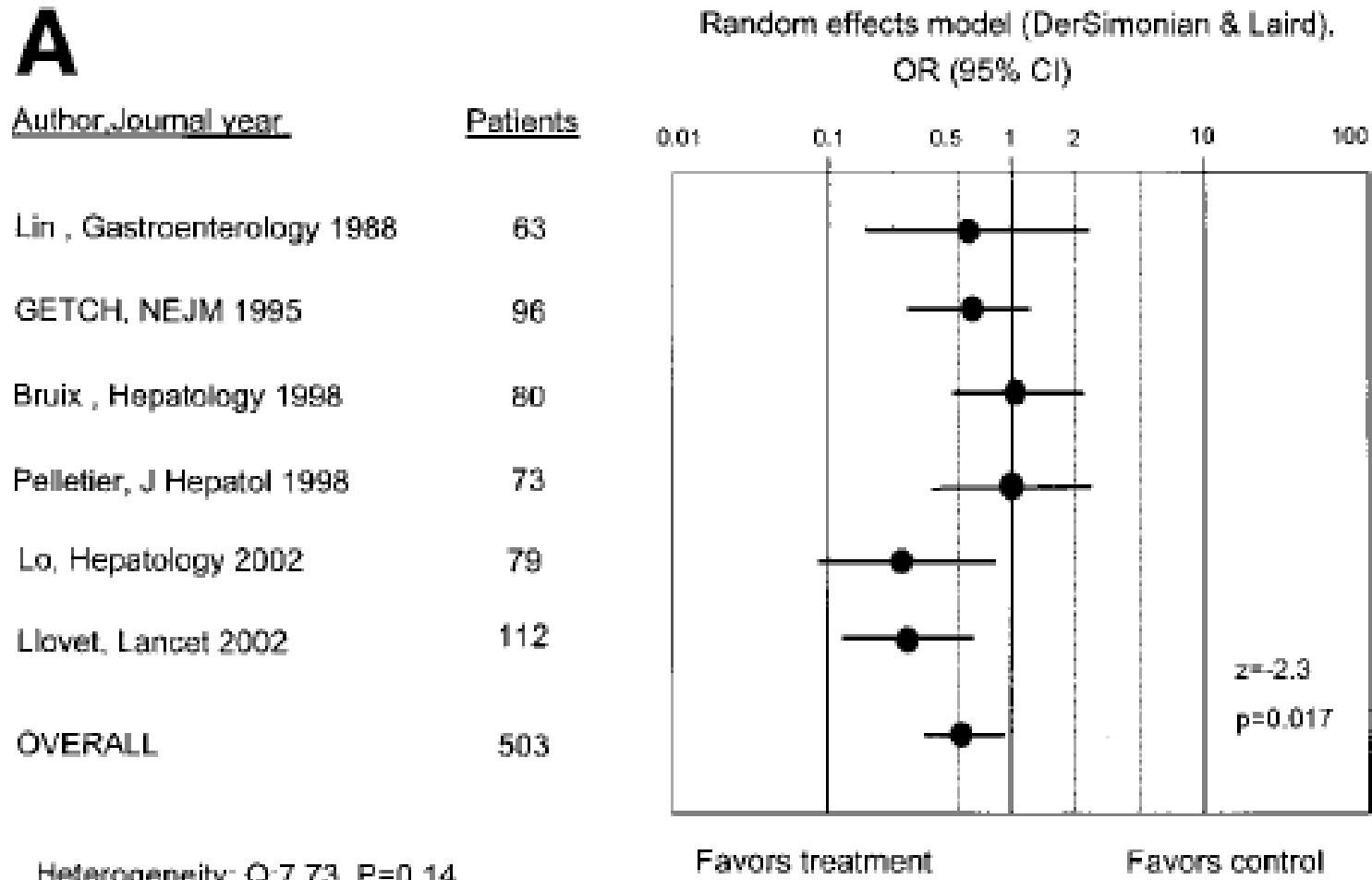
1.000000 deg

Revolution-time: 0.8000000119209

Pitch: 0

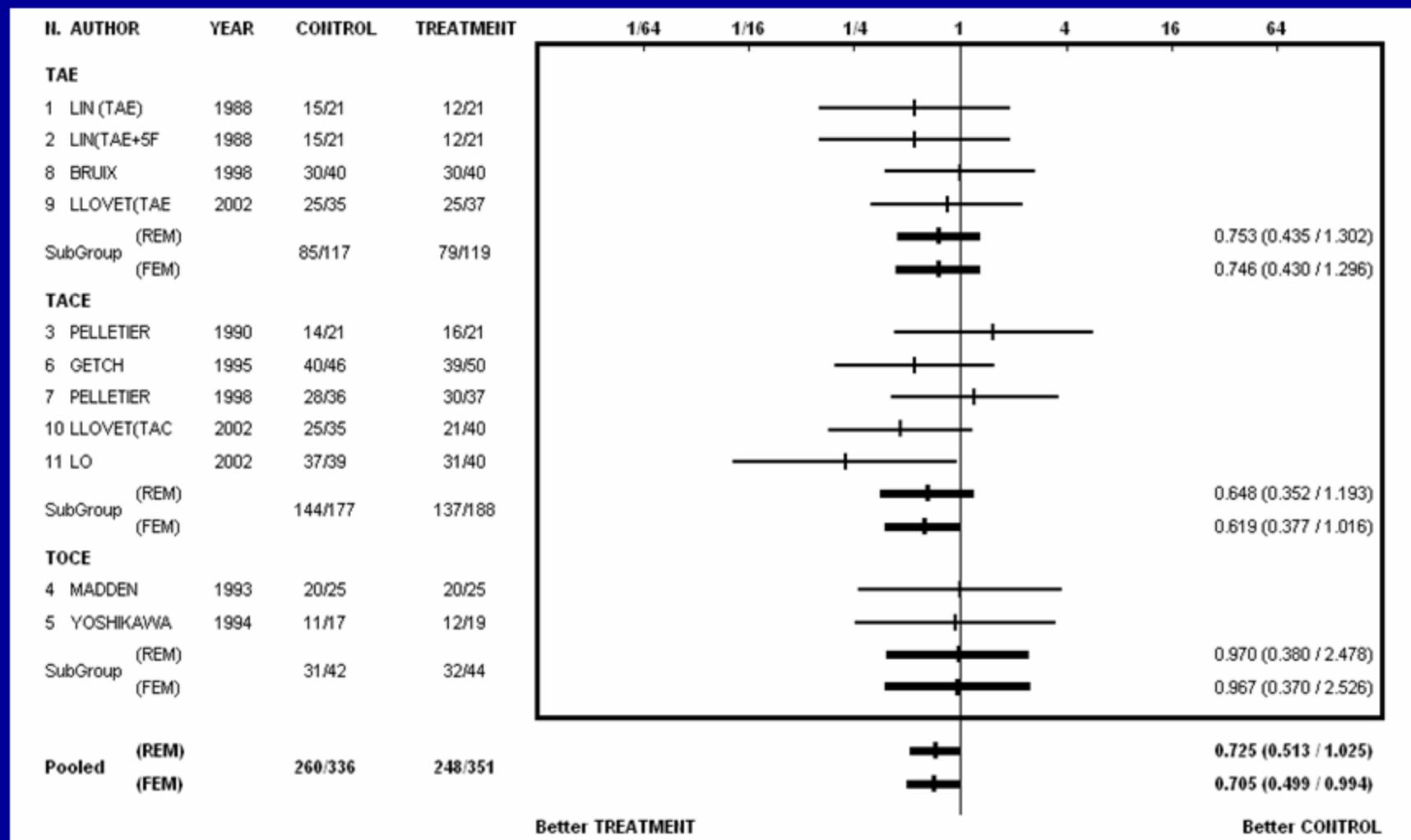
Meta-analysis of RCTs comparing 2-year survival with TACE/TAE versus conservative management or suboptimal therapies for unresectable HCC Llovet&Bruix 2003

A



(OR, 0.53; 95% CI, 0.32-0.89; P .017)

Sensitivity analyses comparing different transarterial techniques: embolization (TAE), chemoembolization (TACE) and lipiodolization (TOCE) for survival.



Marelli 2007

Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma Oliveri RS, Wetterslev J, Gluud C. Cochrane Database Syst Rev 2011;3:CD004787

- Meta-analysis of trials with low risk of selection bias showed that TACE or TAE versus control does not significantly increase survival (HR 0.88; 95% CI 0.71–1.10).
- Two trials with low risk of selection bias, no early stopping, and no co-intervention did not establish any significant effect of TACE or TAE on overall survival (hazard ratio 1.22, 95% confidence interval 0.82–1.83; P = 0.33).
- Trial sequential analysis confirmed the absence of evidence for a beneficial effect of TACE or TAE on survival indicating the need for future randomisation of up to 383 additional participants.
- Substantial differences in criteria for assessing tumor response did not allow quantitative analyses.

Limitations of the Oliveri's meta-analysis

Forner A et al J Hepatol 2012;56:984-6

-Therefore, by including trials not targeting the proper population and treatment strategy, and trials including patients that do not fit into the accepted profile for TACE, the meta-analysis turned negative.
- stratification into different subgroups according to bias or other criteria prevented to reach the needed strength of the data, while the low-profile trials were still used.
- when willing to estimate the sample size that would be required for robust assessment, it appears that Oliveri et al. have used a very modest expectation in survival improvement: 10%.

Patients with Intermediate (BCLC B) HCC: Proposal for a Subclassification

Bolondi et al 2012

BCLC Sub-Stage	B1	B2	B3	B4
CPT score	5-6-7	5-6	7	8-9*
Beyond Milan and within Ut-7	IN	OUT	OUT	ANY
ECOG (Tumor Related) PS	0	0	0	0-1
PVT	NO	NO	NO	NO
1st option	TACE	TACE or TARE		BSC
Alternative	LT TACE + ablation	SOR	Research trials TACE SOR	LT**

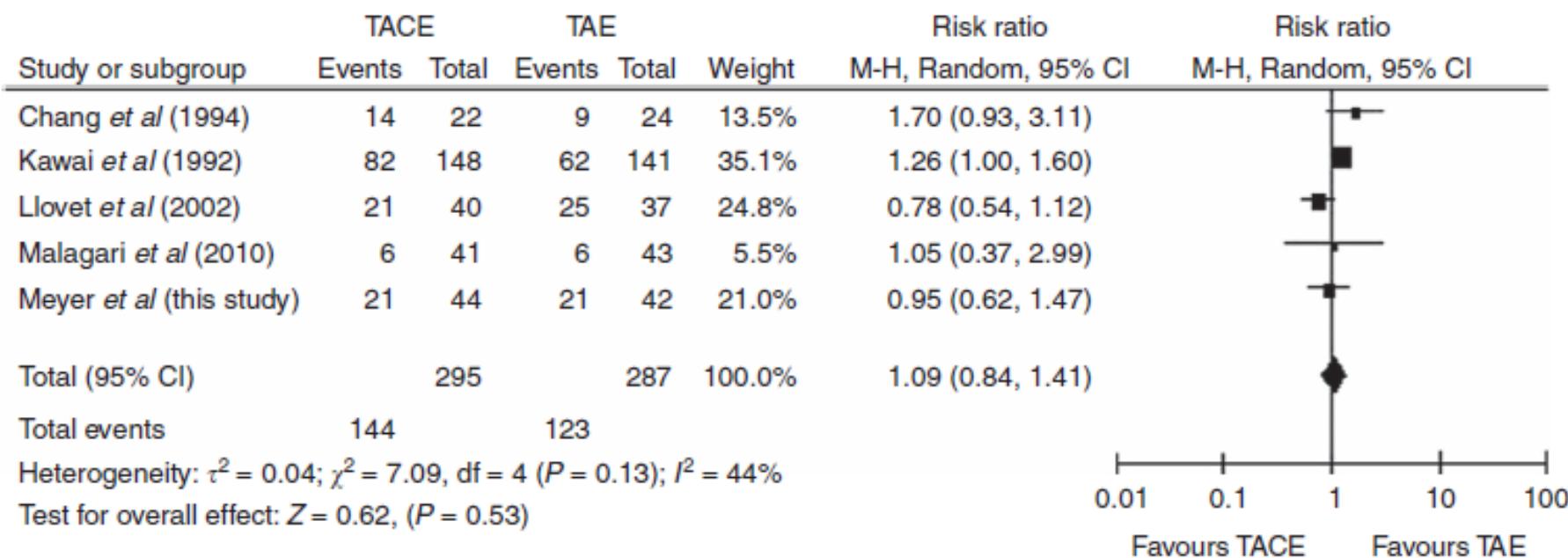
Intermediate stage, but with undetermined peripheral portal vein thrombosis

Stage	Quasi-C
CPT class/score	A
Beyond Milan and within Ut-7	ANY
ECOG (Tumor Related) PS	0
PVT	YES (segmentary or subsegmentary)
1st option	SOR
Alternative	TACE or TARE

Survival outcomes following TACE or TAE alone

Meyer T et al British Journal of Cancer (2013), 1–8

| doi: 10.1038/bjc.2013.85



Treatment results: Y90 radioembolization for HCC

B

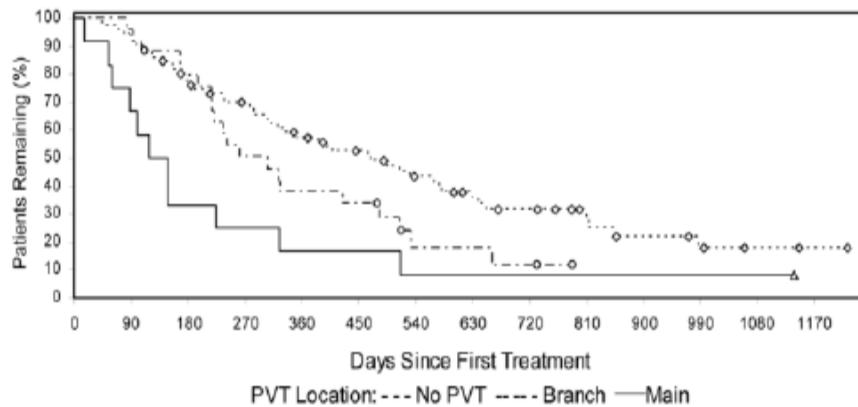


Fig. 1. Overall Kaplan-Meier survival.

(HEPATOLOGY 2008;47:71-81.)

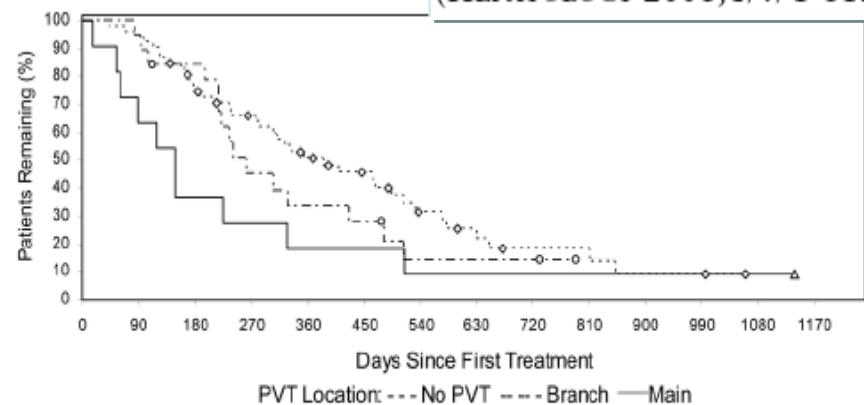


Fig. 2. Kaplan-Meier survival between date of first treatment and PVT location—patients with cirrhosis.

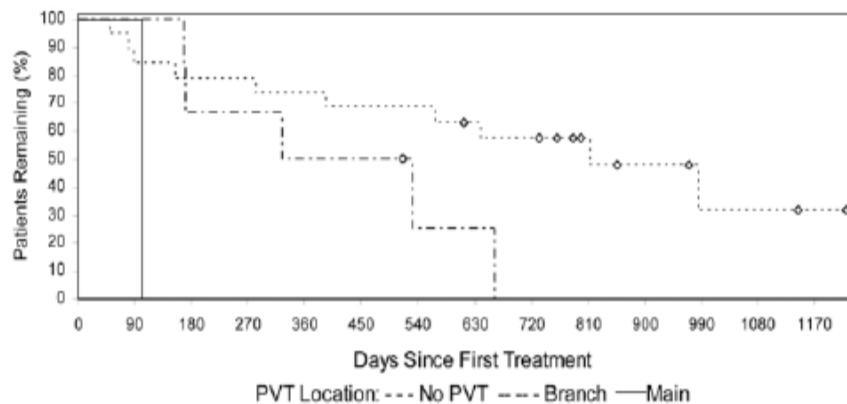


Fig. 3. Kaplan-Meier survival between date of first treatment and PVT location—patients without cirrhosis.

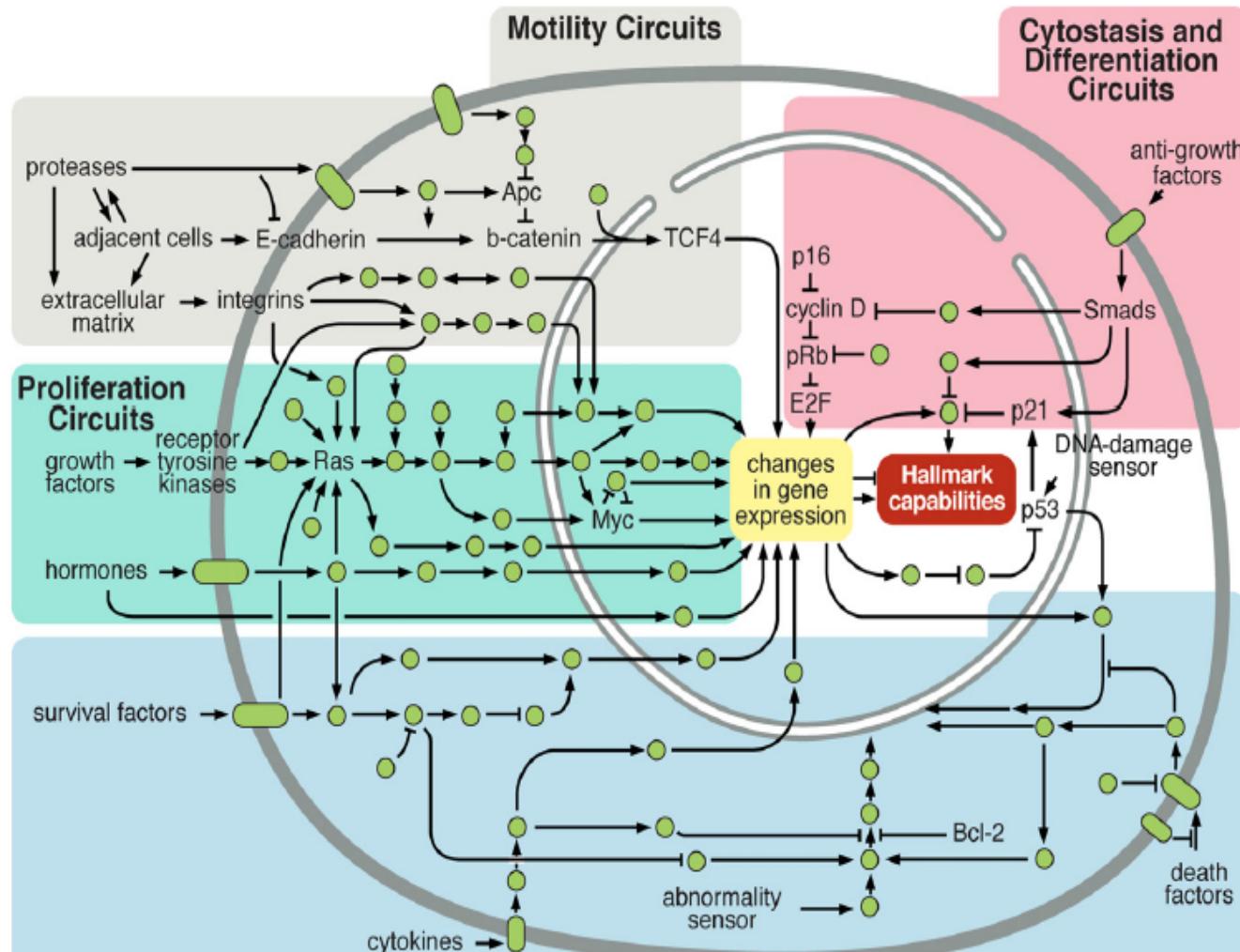
Reported evidence

- Kulik et al, Hepatology 2008;47:71-81
 - 108 patients with advanced HCC ,37 with imaging proving PVT
 - Cumulative dose administered :139,7Gy (131,9 Gy in pts with PVT)
 - Liver related adverse events :jaundice 40%, ascites 18%, HE 4% in pts with cirrhosis and PVT (4%,4%,0% respectively in pts without)
 - Tumor response :WHO/EASL criteria 42,2 % /70 %
 - Median survival from the date of the first treatment for patients without cirrhosis or PVT :813 d
 - In patients with branch PVT, 304 d (**Cirrhotics** :261 d, **non-Cir** :427 d)
 - Y90 microspheres are safe and effective treatment in HCC, even with PVT
 - Glass microspheres did not result in a macroembolic effect

Selected recent reviews

- Current status of hepatocellular carcinoma treatment in Japan: transarterial chemoembolization. Matsui O. Clin Drug Investig. 2012 Aug;32 Suppl 2:3-13.
- Chemoembolization for hepatocellular carcinoma. Lencioni R. Semin Oncol. 2012 Aug;39(4):503-9.
- Transarterial therapies for hepatocellular carcinoma.
Tsochatzis EA, Fatourou EM, Triantos CK, Burroughs AK. Recent Results Cancer Res. 2013;190:195-206.
- Management of hepatocellular carcinoma with transarterial chemoembolization in the era of systemic targeted therapy. Lencioni R. Crit Rev Oncol Hematol. 2012 Aug;83(2):216-24.

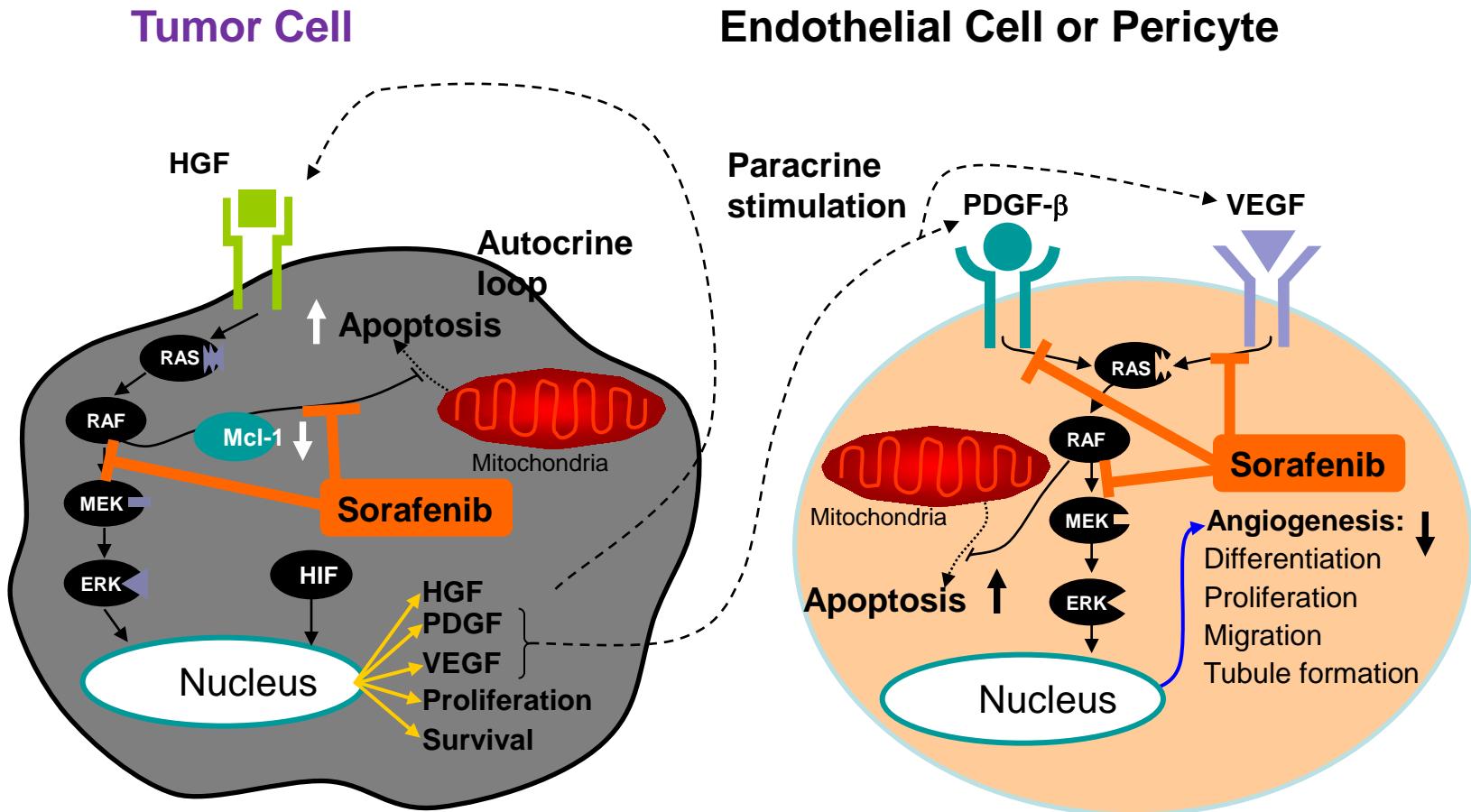
Οδοί και δίκτυα ενδοκυττάριων σημάτων του καρκινικού κυττάρου



Hanahan D. and Weinberg RA,
Cell 2011;144:646-674

Viability Circuits

Sorafenib Targets Tumor Cell Proliferation and Angiogenesis

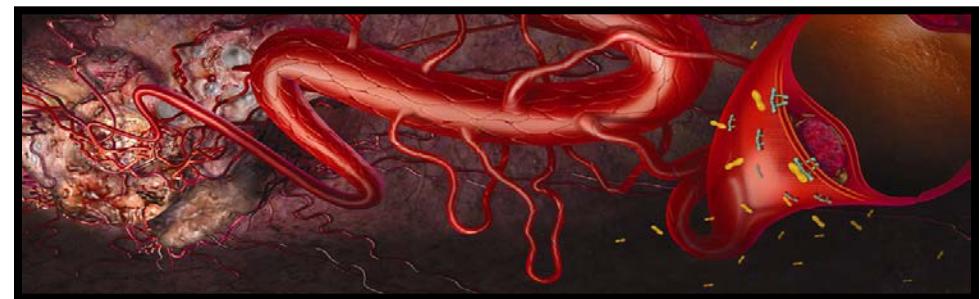


HGF = hepatocyte growth factor.

Avila MA, et al. Oncogene. 2006;25:3866-3884; Liu L, et al. Cancer Res. 2006;66:11851-11858;
Semela D, et al. J Hepatol. 2004;41:864-880; Wilhelm SM, et al. Cancer Res. 2004;64:7099-7109.

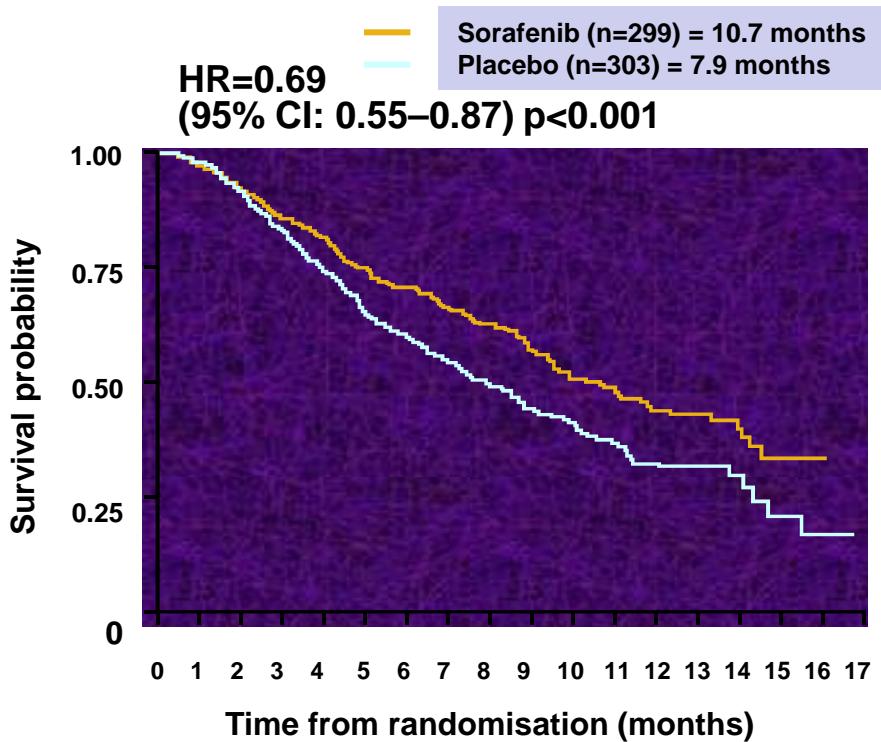
Η Αγγειογένεση στη προοδευτική εξέλιξη του ΗΚΚ

- Αγγειογενετικοί παράγοντες με επίπτωση στην εξέλιξη του ΗΚΚ
 - VEGFs (vascular endothelial growth factors)
 - PDGFs (platelet-derived growth factors)
 - PIGF (placental growth factor)
 - TGF- α , TGF- β (transforming growth factors-alpha, -beta)
 - bFGF (basic fibroblast growth factor)
 - EGF (epidermal growth factor)
 - HGF (hepatocyte growth factor)
 - ANGs (angiopoietins)
 - IL-4, IL-8 (interleukins-4, -8)

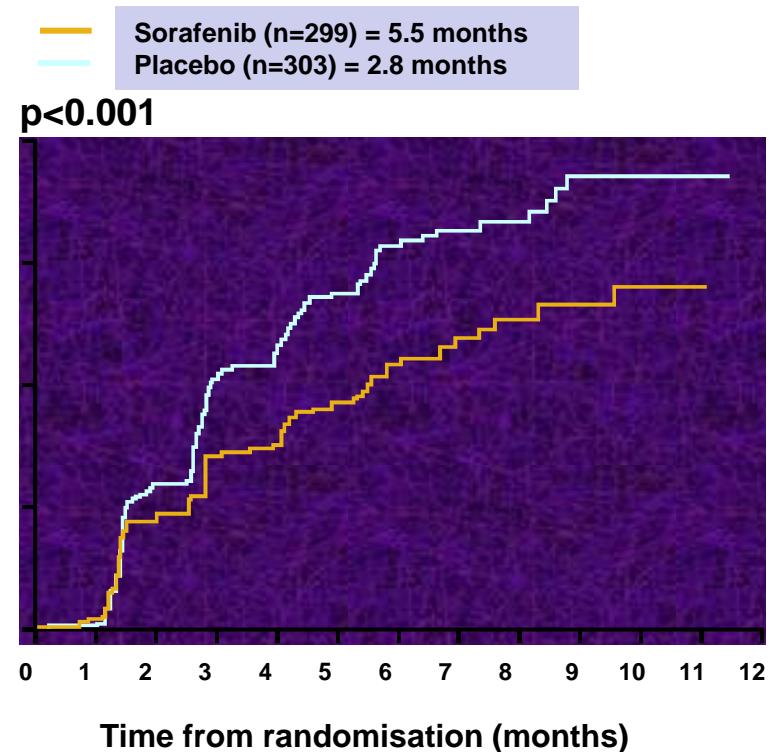


SHARP Phase III Trial in Advanced HCC: Sorafenib prolongs OS by 44% and TTP by 74%

Overall Survival



Time to Progression (independent central review)



SHARP: Drug-Related AEs are Primarily Grade 1/2, Predictable, and Manageable

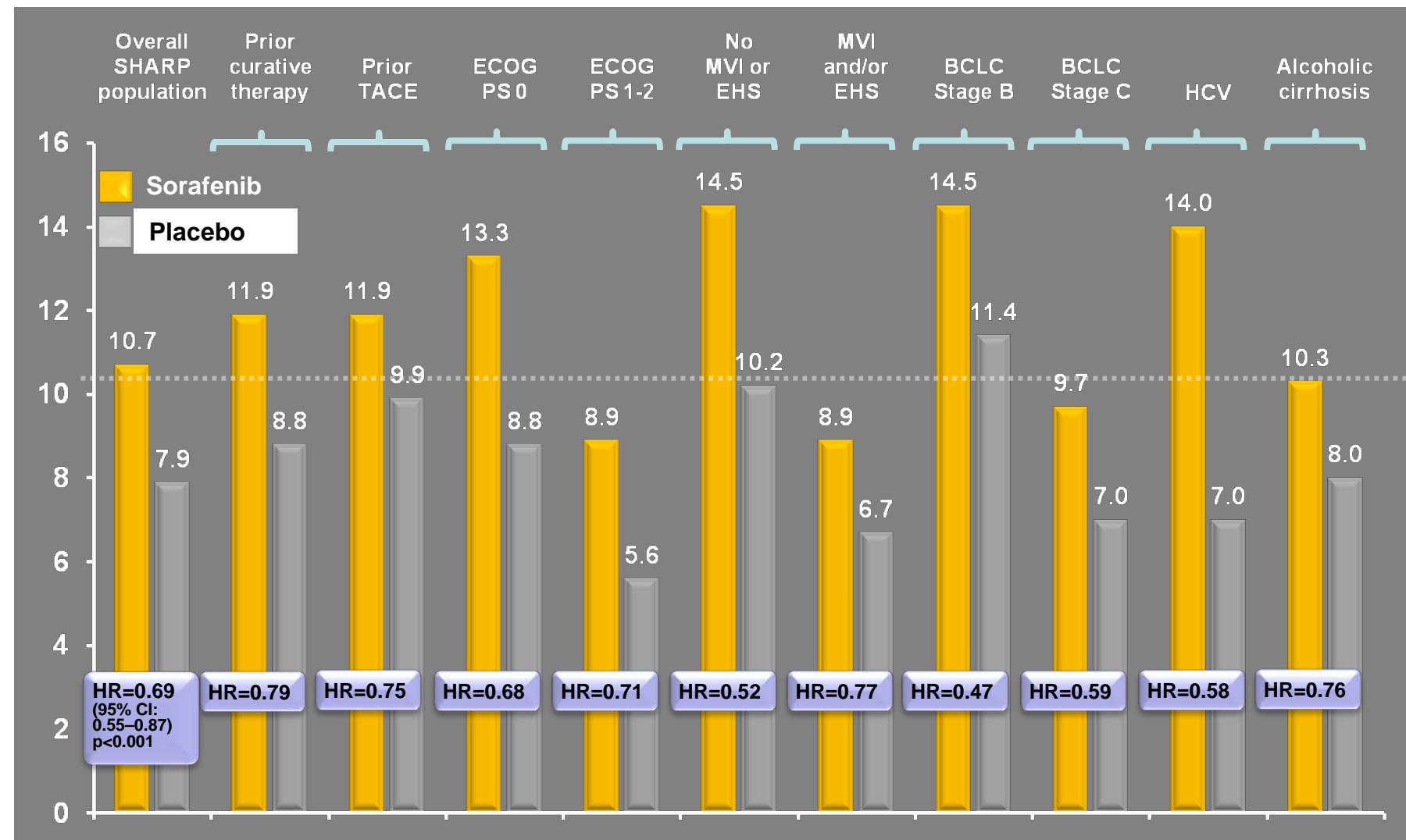
Incidence by Grade (%)

Sorafenib (n=297)

Placebo (n=302)

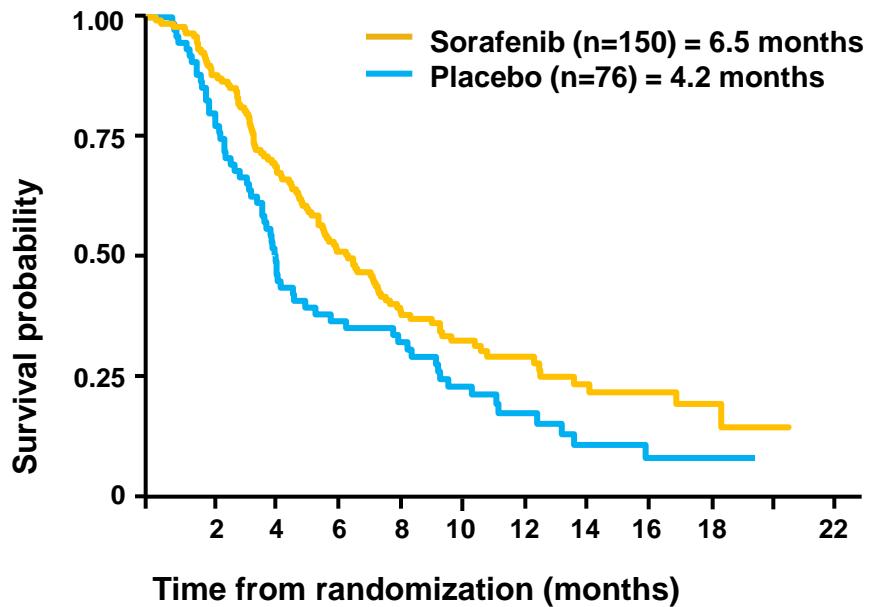
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Overall incidence	80			52		
Diarrhea (P<0.001)	39	8	0	11	2	0
Fatigue	22	3	1	16	3	<1
HFSR (P<0.001)	21	8	0	3	<1	0
Rash / desquamation	16	1	0	11	0	0
Anorexia	14	<1	0	3	1	0
Alopecia	14	0	0	2	0	0
Nausea	11	<1	0	8	1	0
Weight loss (P=0.03)	9	2	0	1	0	0
Pruritis	8	0	0	7	<1	0
Dry skin	8	0	0	4	0	0
Pain, abdomen NOS	8	2	0	3	1	0
Bleeding	7	1	0	4	1	<1
Voice changes	6	0	0	1	0	0
Vomiting	5	1	0	3	1	0
Hypertension	5	2	0	2	1	0
Dermatology, other	5	1	0	1	0	0
Liver dysfunction	<1	<1	0	0	0	0

Sorafenib Prolongs Survival in Advanced HCC Irrespective of Patient Characteristics or Extent of Disease

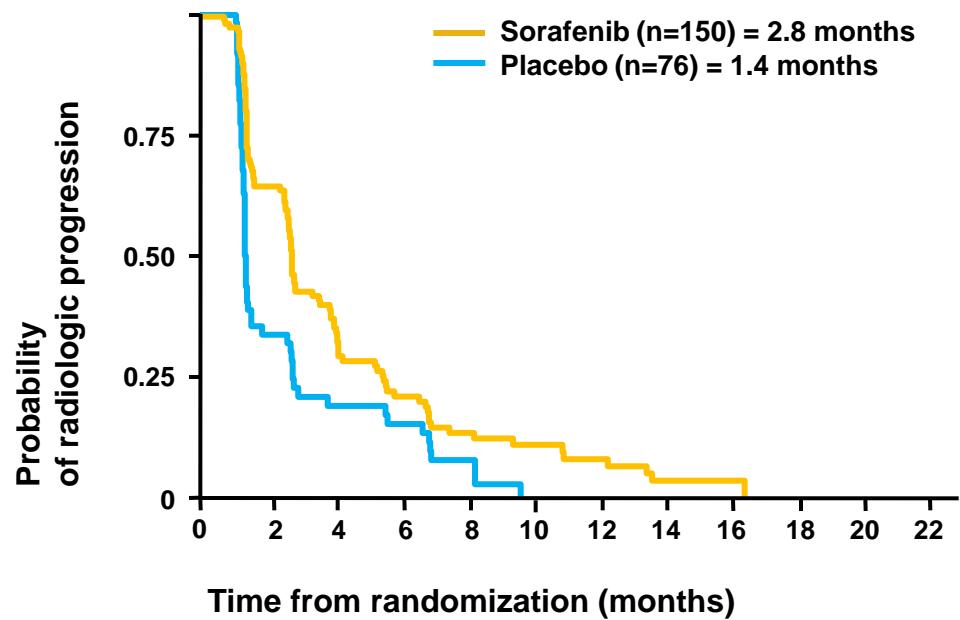


Asia-Pacific Phase III Trial in Advanced HCC: Sorafenib prolongs OS by 47% and TTP by 74%

Overall Survival



Time to Progression



Incidence of Drug-Related Adverse Events in Asia-Pacific Trial

Drug-related AEs*	Incidence by Grade (%)		Placebo (n=75)		
	Sorafenib (n=149)	Any	3/4	Any	3/4
HFSR	45	11		3	0
Diarrhea	26	6		5	0
Alopecia	25	—		1	—
Fatigue	20	3		8	1
Rash/desquamation	20	1		7	0
Hypertension	19	2		1	0
Anorexia	13	0		3	0
Nausea	11	1		11	1

*Events occurring in at least 10% of patients in either arm
Incidence of AEs were comparable to those observed in the SHARP trial

Sorafenib in Patients with Child-Pugh B Liver Dysfunction

- **Majority of sorafenib clinical data are for Child–Pugh A patients¹**
- In a phase II study, sorafenib tolerability was similar in patients with Child–Pugh A or B liver function²
- No dose adjustment is required in Child–Pugh B patients (EU SmPC) ¹
- Sorafenib is recommended for patients with advanced HCC and Child–Pugh A or B status:
 - National Comprehensive Cancer Network (NCCN) guidelines for HCC 3
 - Asian Pacific Association for the Study of the Liver (APASL) consensus statement on HCC⁴
- **Until more data are available, caution is required when treating Child–Pugh B patients with sorafenib^{4–6}**

1. sorafenib EU SmPC; 2. Abou-Alfa GK, et al. ASCO 2008, 3. NCCN Clinical Practice Guidelines in Oncology – Hepatobiliary Cancers. V.1.2009

4. Asian Pacific Association for the Study of the Liver consensus statement on HCC, February 2009, 5. Wörns MA, et al. J Clin Gastroenterol 2009 Feb 25 [Epub];

6. Zhu AX, Clark JW. Oncologist 2009;14:67–9

Testing Sorafenib in all stages of HCC

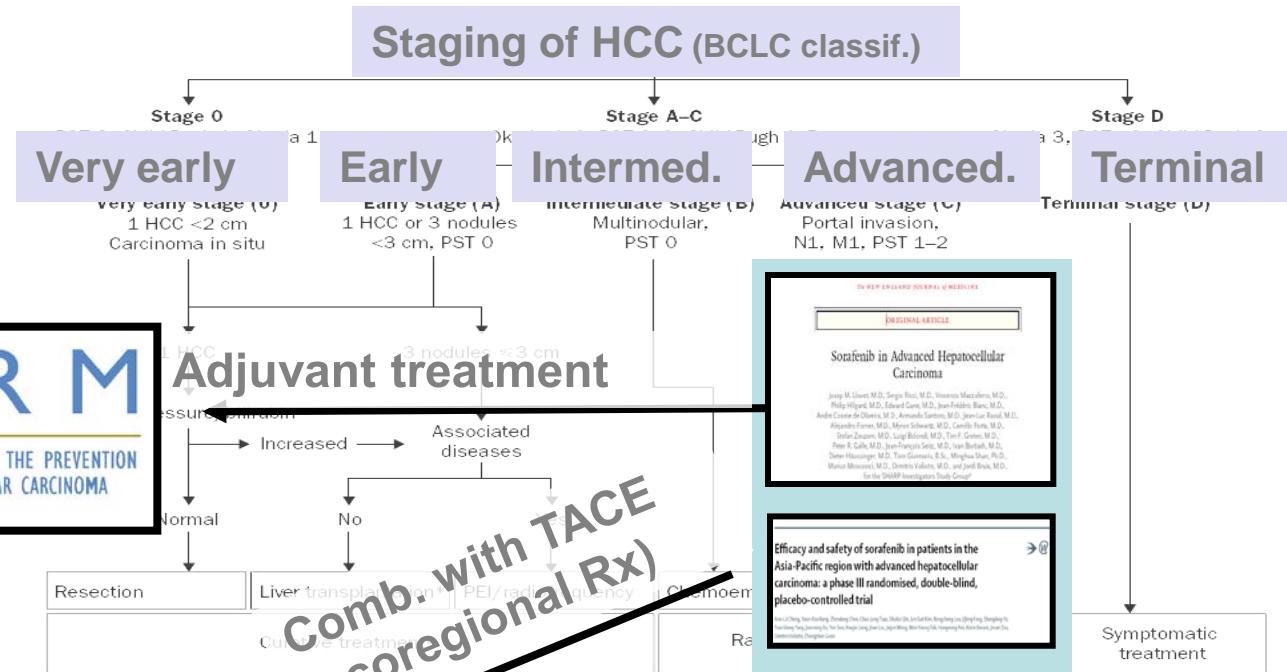
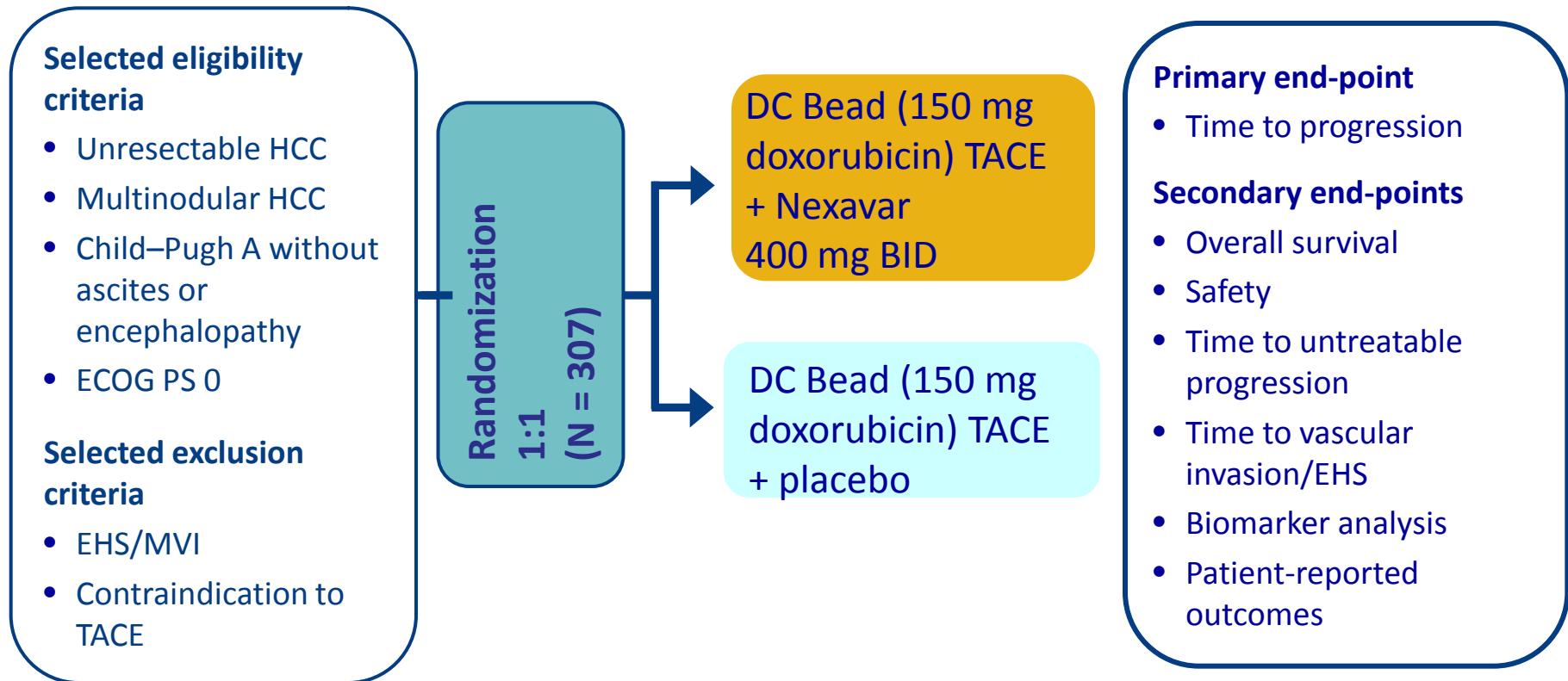


Figure 5: Barcelona-Clinic Liver Cancer staging classification and treatment schedule
PST=performance status test. N=nodes. M=metastases. PEI=percutaneous ethanol injection. *Cadavaric liver transplantation references 54 and 40 with permission from The American Association for the Study of Liver Diseases.



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SPACE(II): Nexavar or Placebo in Combination with TACE for Intermediate-Stage HCC



- **Phase II**, randomized, double-blind, placebo-controlled study of **Nexavar or placebo in combination** with TACE, performed with DC Bead® TACE (DEBDOX) and doxorubicin for intermediate-stage HCC **J Clin Oncol 2012;suppl.LBA154**

TACE with or without systemic therapy?

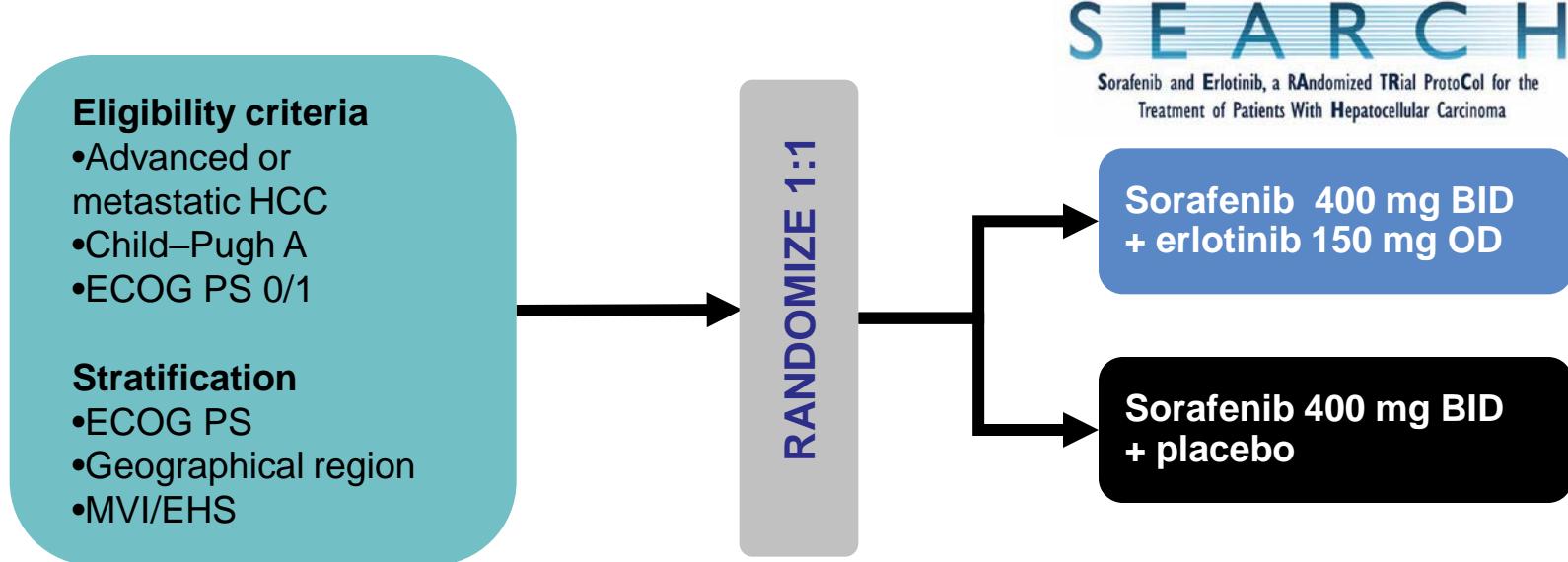
JF Dufour (Edit) J Hepatol 2012;56:1224

- ECOG E1208 phase III (NCT01004978)
- TACE 2 phase III (NCT01324076)
- Brivanib (NCT00908752)
- Everolimus (NCT01009801)
- **SPACE (II), n=307 HR 0.797**
- **Median TTP 169 vs 166 days** (J Clin Oncol 2012;suppl.LBA154)

HCC: sorafenib/erlotinib combination therapy

Phase III study (SEARCH)

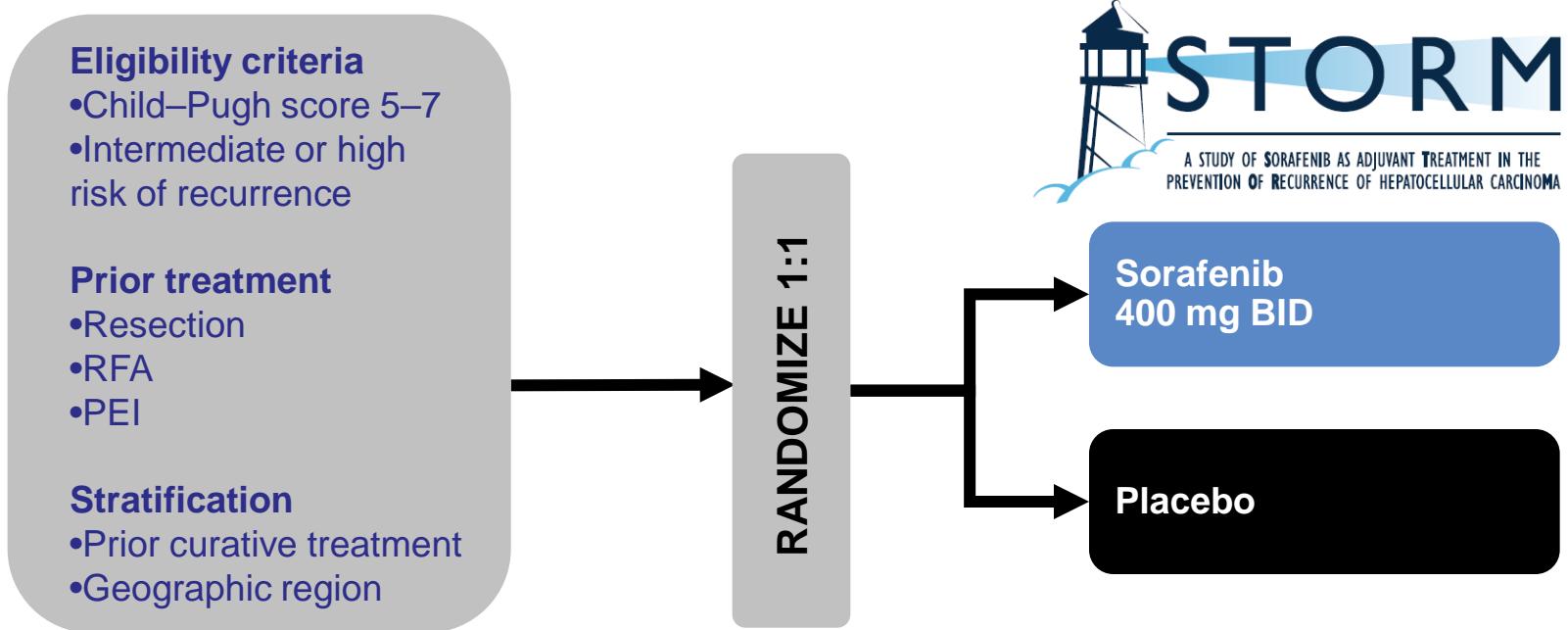
- International (Europe, Americas, Asia–Pacific, Japan), Phase III, double-blind, placebo-controlled trial



- n = 730
- Primary endpoint: OS
- Secondary endpoints: TTP, DCR, PRO, safety, biomarkers

HCC: STORM is addressing unmet need for adjuvant therapy in HCC

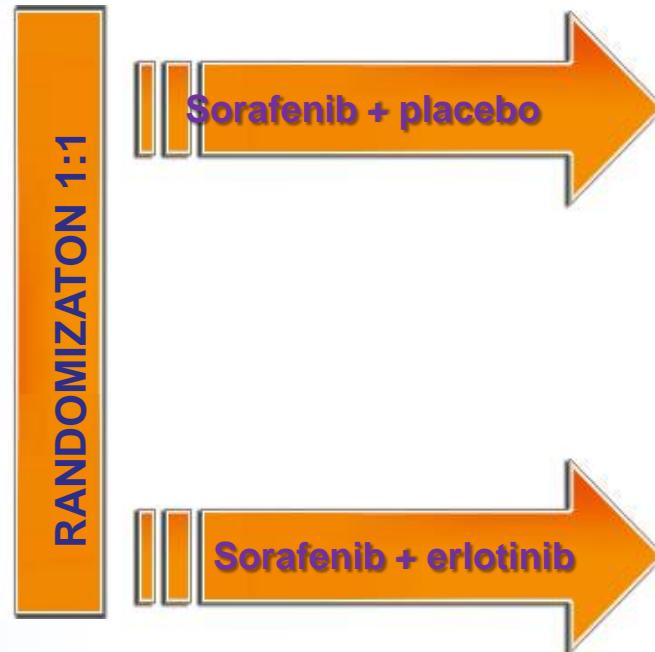
- International (Europe, Americas, Asia–Pacific, Japan), Phase III, double-blind, randomized, placebo-controlled adjuvant trial



- n = 1115
- Primary endpoint: recurrence-free survival
- Secondary endpoints: time to recurrence, OS, QoL, biomarkers

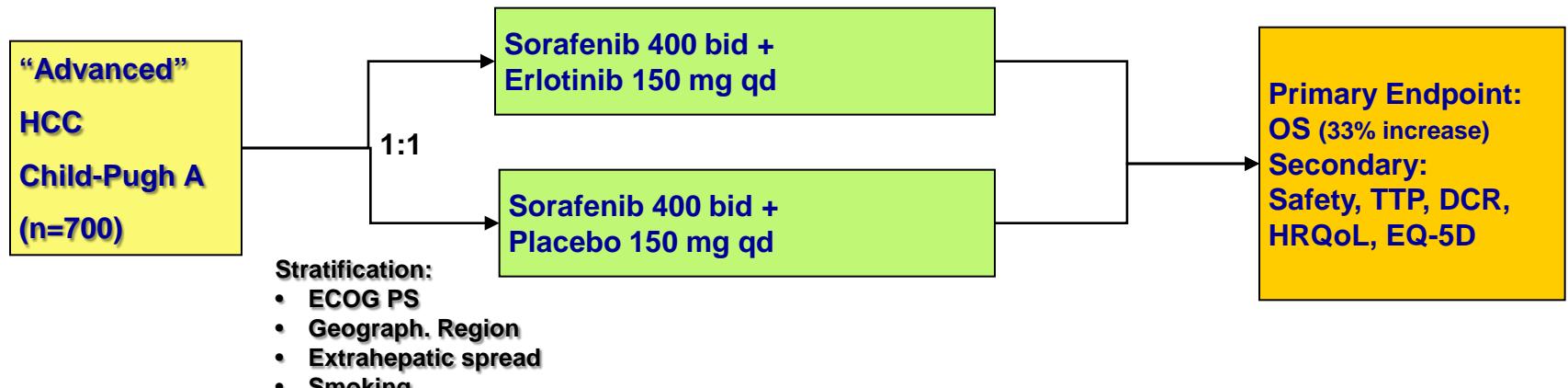
Study Design

- Unresectable Advanced or Metastatic HCC
- Child Pugh A status
- ECOG PS: 0 or 1
- Stratification:
 - ECOG PS
 - MVI/EHS
 - Geography
 - Smoking Status



Primary Endpoint
Overall Survival (OS)

Study Design



**Overview of
Sorafenib
use in combination
in HCC:**



Overview of safety events (Safety population N=417)

Treatment Emergent AEs	397 (95.2%)
Treatment Emergent SAEs	170 (40.8%)
AEs leading to withdrawal	101 (24.2%)
AEs leading to dose reduction	136 (32.6%)

Incidence of Treatment Emergent AEs (all grades) for ≥ 10% subjects by Event (1 of 2)

(Safety population N=417)

Gastrointestinal	
Diarrhea	56.6%
Anorexia	33.8%
Nausea	19.9%
Mucositis	16.1%
Vomiting	16.1%
Constipation	12.2%
Ascites	10.3%
Constitutional	
Fatigue	42.0%
Weight loss	18.0%
Fever	16.5%
Dermatology/Skin	
Rash/Desquamation	39.1%
Hand-Foot skin reaction	37.9%
Alopecia	14.9%

Incidence of Treatment Emergent AEs (all grades) for \geq 10% subjects by Event (2 of 2) (Safety analysis set N=417)

Pain	
Pain, abdomen NOS	23.5%
Cardiac general	
Hypertension	17.3%
Metabolic/Laboratory	
AST	16.8%
Bilirubin/Hyperbilirubinemia	14.6%
ALT	10.1%
Lymphatics	
Edema, Limb	12.2%
Blood/bone marrow	
Hemoglobin	11.0%
Pulmonary/upper respiratory	
Cough	10.1%

Incidence of Treatment Emergent AEs leading to Withdrawal by Event * (Safety population N=417)

	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any event	24.2%	1.2%	2.6%	13.4%	3.4%	3.6%
Liver dysfunction	3.1%		0.5%	0.2%	1.0%	1.4%
Diarrhea	2.4%	0.5%		1.7%	0.2%	
Fatigue	2.4%			2.2%	0.2%	
HFSR	2.2%	0.2%	0.7%	1.2%		

* Only events with incidence $\geq 2.0\%$ are included in this table

Incidence of Treatment Emergent SAEs reported by Event * (Safety population N=417)

	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any event	40.8%	0.7%	4.6%	19.9%	4.6%	10.8%
Liver dysfunction	6.2%		0.2%	1.9%	0.7%	3.4%
Fever	3.4%	1.4%	1.7%	0.2%		
Diarrhea	2.4%		0.2%	1.7%	0.5%	
Death, disease progression	2.4%					2.4%
Pain, abdomen NOS	2.2%		0.2%	1.9%		
Constitutional- others	2.2%	0.2%		1.0%	0.2%	0.7%
Hemoglobin	2.2%	0.2%	0.7%	0.5%	0.7%	

* Only events with incidence $\geq 2.0\%$
are included in this table

Incidence of Treatment Emergent AEs leading to dose reduction by Event *(Safety population N=417)

	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any event	32.6%	1.2%	2.6%	27.6%	1.2%	
HFSR	9.6%	0.5%	0.7%	8.4%		
Diarrhea	5.0%	0.5%	1.2%	3.4%		
Rash/desquamation	3.1%	0.5%	0.5%	2.2%		
Fatigue	2.9%	0.7%	0.2%	1.9%		

* Only events with incidence $\geq 2.0\%$
are included in this table

Phase 3 trials testing molecular therapies in HCC

Author	Journal	Year	Therapeutic line	n	Drug (targets)	Primary endpoint	OS* (mo)	PFS* (mo)	TTP* (mo)
Llovet	EASL-2012	2012	Second	263	<u>Bribanib</u> (VEGFR, FGFR) Placebo	OS	9.4	---	4.2
				132			8.2		2.7
Cheng	ASCO-2011	2011	First	529	<u>Sunitinib</u> (KIT, VEGFR, PDGFR) <u>Sorafenib</u> (BRAF, VEGFR, PDGFR)	OS	8.1	3.6	4.1
				544			10		4
Cheng	Lancet Oncol	2009	First	150	<u>Sorafenib</u> (BRAF, VEGFR, PDGFR) Placebo	----	6.5	---	2.8
				76			4.2		1.4
Llovet	N Engl J Med	2008	First	299	<u>Sorafenib</u> (BRAF, VEGFR, PDGFR) Placebo	OS/TSP*	10.7	---	5.5
				303			7.9		2.8

Randomized Phase 2 trials

Arai	ASCO-2010	2010	First	50	<u>TSU-68</u> (VEGFR, PDGFR, FGFR) Placebo	PFS	---	5.2	---
				21				4	

Phase 2 trials testing molecular therapies in HCC

Author	Journal	Year	Therapeutic line	n	Drug (targets)	Primary endpoint	OS* (mo)	PFS* (mo)	TTP* (mo)
Finn	Clin Cancer Res	2012	Second	48	<u>Bribanib</u> (VEGFR, FGFR)				
Kaseb	Oncology	2012	First	59	<u>Erlotinib</u> (EGFR) + <u>Bevacizumab</u> (VEGF)	PF-16*	13.7	7.2	---
Yau	Invest New Drugs	2012	Second	10	<u>Erlotinib</u> (EGFR) + <u>Bevacizumab</u> (VEGF)	CB*	4.3	1.5	1.8
Park	Clin Cancer Res	2011	First	55	<u>Bribanib</u> (VEGFR, FGFR)	PF-24	8.9	2.7	2.8
Zhu	Cancer	2011	First	28	<u>Everolimus</u> (MTOR)	PF-24	8.4	3.8	3.9
Alberts	Am J Clin Oncol	2011	First	28	<u>Cediranib</u> (VEGFR)	6-month survival	5.8	---	2.8
O'Neil	J Clin Oncol	2011	First	17	<u>Selumetinib</u> (MEK1/2)	RR	4.2	1.4	1.4
Toh	ASCO-2010	2010	First	44	<u>Linifanib</u> (VEGFR, PDGFR)	PF-16	9.7	---	3.7

Phase 2 trials testing molecular therapies in HCC

Author	Journal	Year	Therapeutic line	n	Drug (targets)	Primary endpoint	OS* (mo)	PFS* (mo)	TTP* (mo)
Kanai	Cancer Chemother Pharmacol	2010	First	35	<u>TSU-68</u> (VEGFR, PDGFR, FGFR)	RR	13.1	---	2.1
Yau	Cancer	2009	First	51	<u>Sorafenib</u> (BRAF, VEGFR, PDGFR)	OS	5	3	---
Ramanathan	Cancer Chemother Pharmacol	2009	First	40	<u>Lapatinib</u> (EGFR, HER2)	RR	6.2	2.3	---
Thomas	J Clin Oncol	2009	First	40	<u>Erlotinib</u> (EGFR) + <u>Bevacizumab</u> (VEGF)	PF-16*	15.7	9	---
Faivre	Lancet Oncol	2009	First	37	<u>Sunitinib</u> (CKIT, VEGFR, PDGFR)	RR	8	---	5.3
Zhu	J Clin Oncol	2009	First	34	<u>Sunitinib</u> (CKIT, VEGFR, PDGFR)	PFS	9.8	3.9	4.1
Bekaii-Saab	Clin Cancer Res	2009	First	26	<u>Lapatinib</u> (EGFR, HER2)	RR	12.6	1.9	

Phase 2 trials testing molecular therapies in HCC

Author	Journal	Year	Therapeutic line	n	Drug (targets)	Primary endpoint	OS* (mo)	PFS* (mo)	TTP* (mo)
Thomas	Cancer	2007	First	40	<u>Erlotinib</u> (EGFR)	PFS	6.25	3.3	6.5
Abou-Alfa et al.	J Clin Oncol	2006	First	137	<u>Sorafenib</u> (BRAF, VEGFR, PDGFR)	RR	9.2	---	5.5
O'Dwyer	ASCO-2006	2006	First	31	<u>Gefitinib</u> (EGFR)	PFS	6.5	2.8	---
Philip	J Clin Oncol	2005	First	38	<u>Erlotinib</u> (EGFR)	PF-24*	13	---	3.2

Research challenges for personalized medicine approaches in HCC

- Oncogene addiction loops
 - improve sorafenib in first line
 - biomarkers of response
 - trial enrichment
- Map HCC heterogeneity/complexity
 - subclones and metastasis
 - circulating tumor cells
 - functional imaging
- Tumor dynamics
 - resistance to sorafenib
 - chemoprevention
 - integrating Personal Omics Profiling (iPOP)

