First International Course of Translational Hepatology
"Focus on HCV Disease"
Firenze, 9-11 march 2011

Liver Transplantation and other therapies in HCV+ patients with liver tumours

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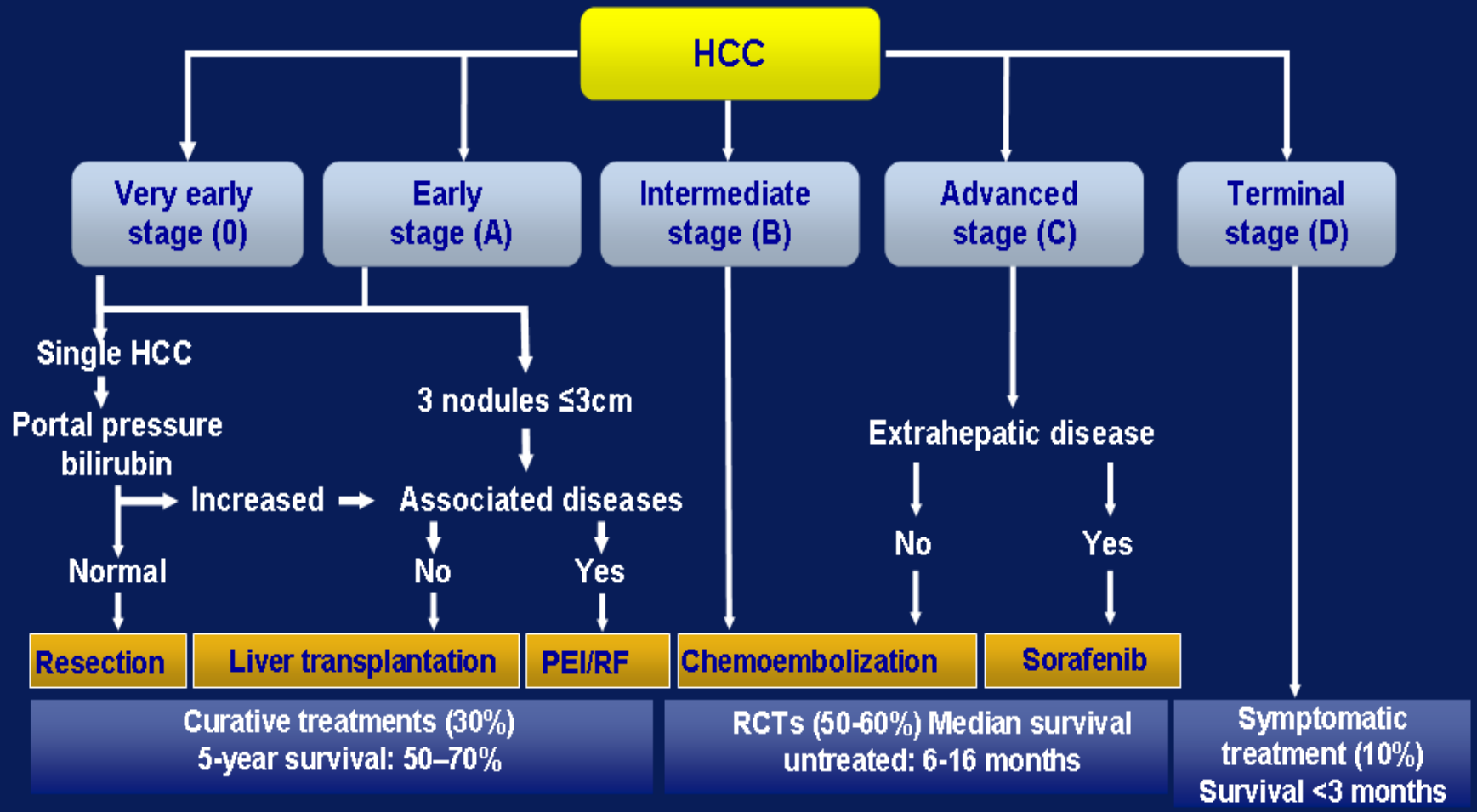
ROYAL FREE & UNIVERSITY COLLEGE MEDICAL SCHOOL

Outline of talk

- Current approach to therapy of HCC
- Liver transplantation for HCC
- Staging of HCC and liver transplantation
- Adjuvant therapy for HCC pre-liver transplant
- Other therapies
- Potential future therapies

Current approach to therapy of HCC

BARCELONA STAGING STRATEGY



Adapted from Llovet JM et al, Lancet 2003;362:1907–1917

The Barcelona Clinic Liver Cancer (BCLC) Staging System

Stage	PS	Tumor stage	Child-Pugh
A. Early	0	Single < 5 cm 3 nodes < 3 cm	A & B
B. Intermediate	0	Large/multinodular	A & B
C. Advanced	1-2	Vascular invasion extrahepatic spread	A & B
D. End-stage	3-4	Any of the above	C

Llovet JM et al Sem Liv Dis 1999;19:329

Liver transplantation for HCC

Liver transplantation as therapy for HCC in cirrhosis

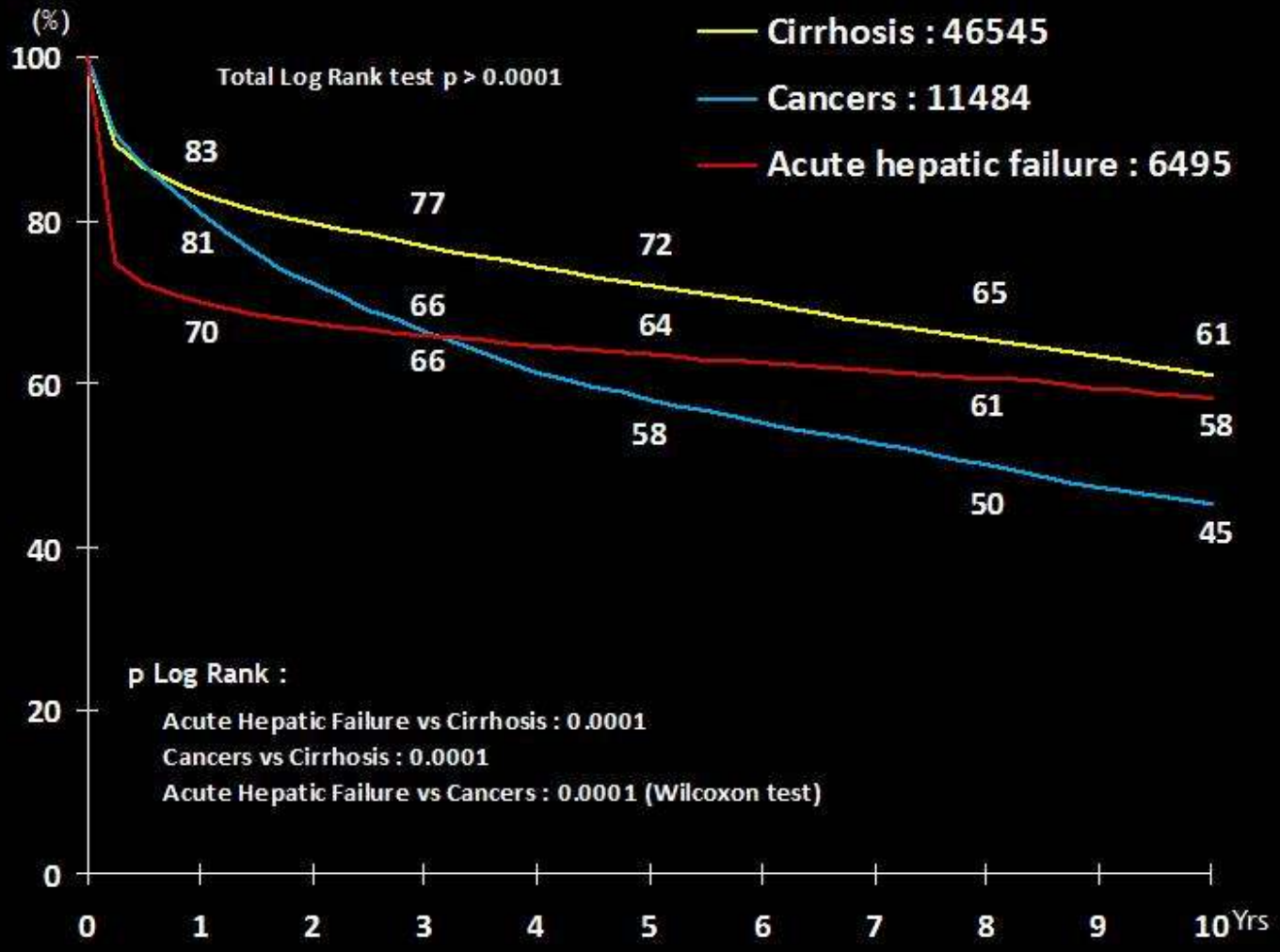
- Removes the tumour
- Prevents metachronous lesions
- Removes the cirrhosis

- Not immediate therapy
- Risk of surgery
- Risk of recurrence

Patient Survival according to the Indication

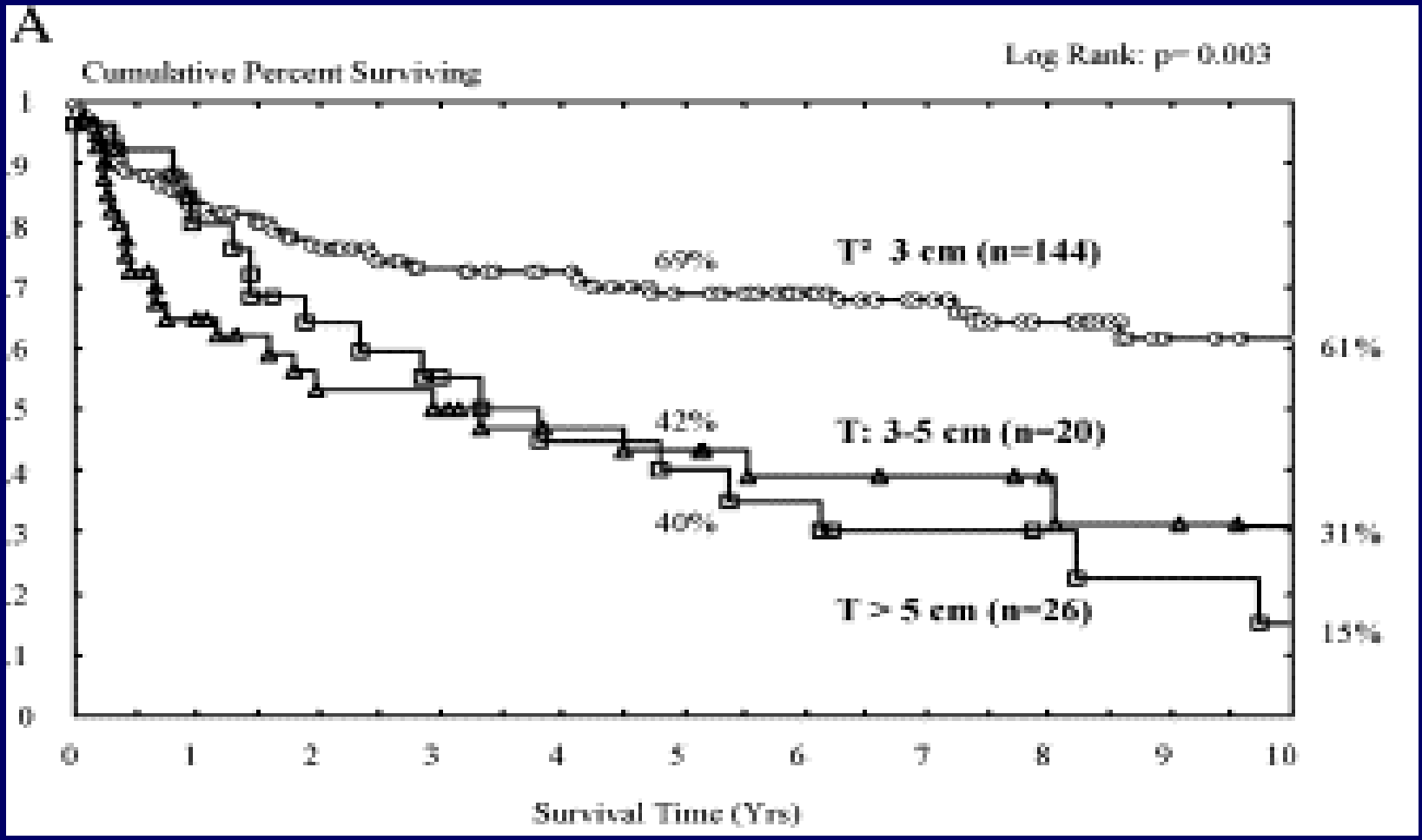
01/1988 - 12/2009

12/2009

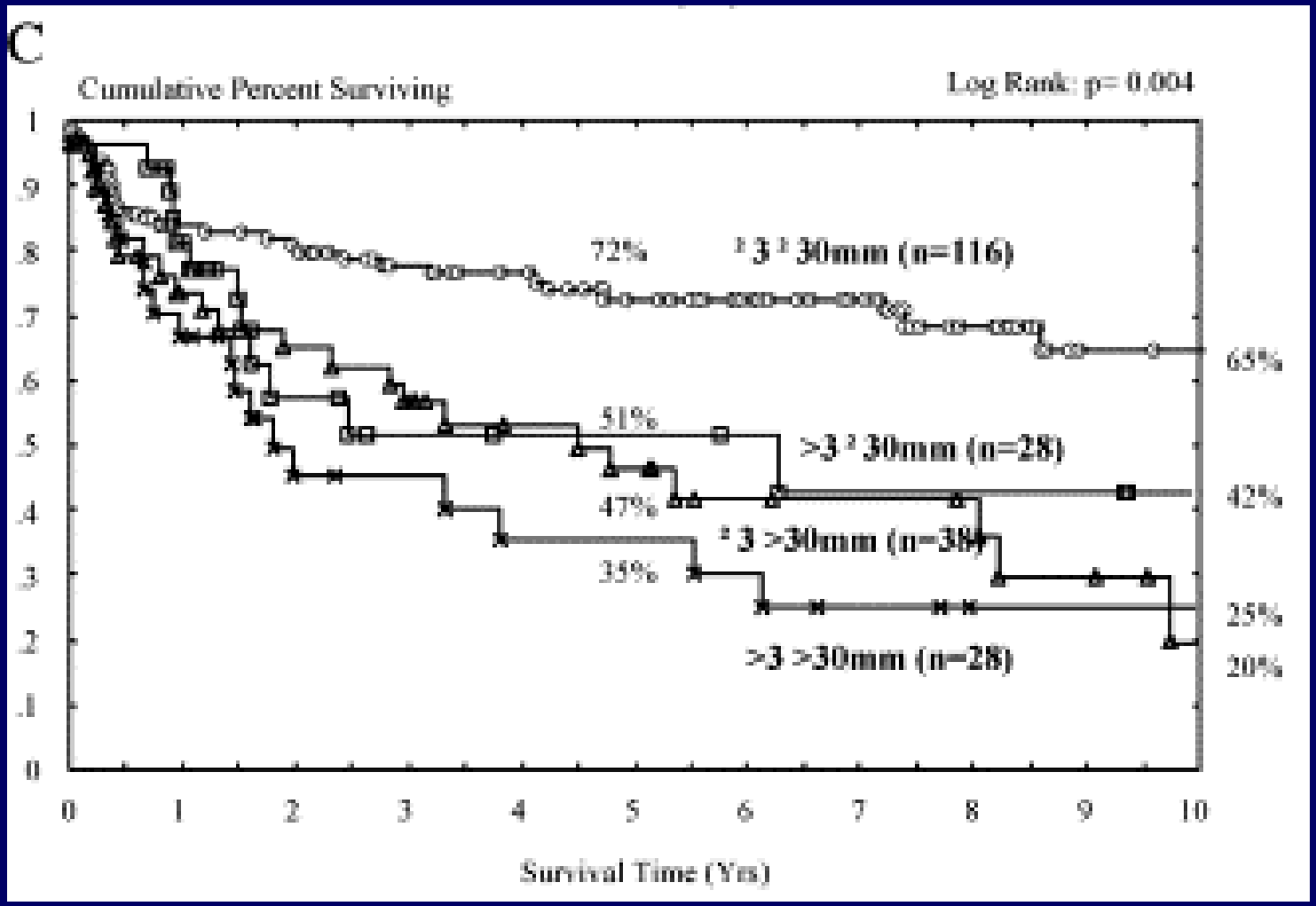


Staging of HCC and liver transplantation

Liver transplant and HCC: maximum size of nodule and survival (Adam 2003)

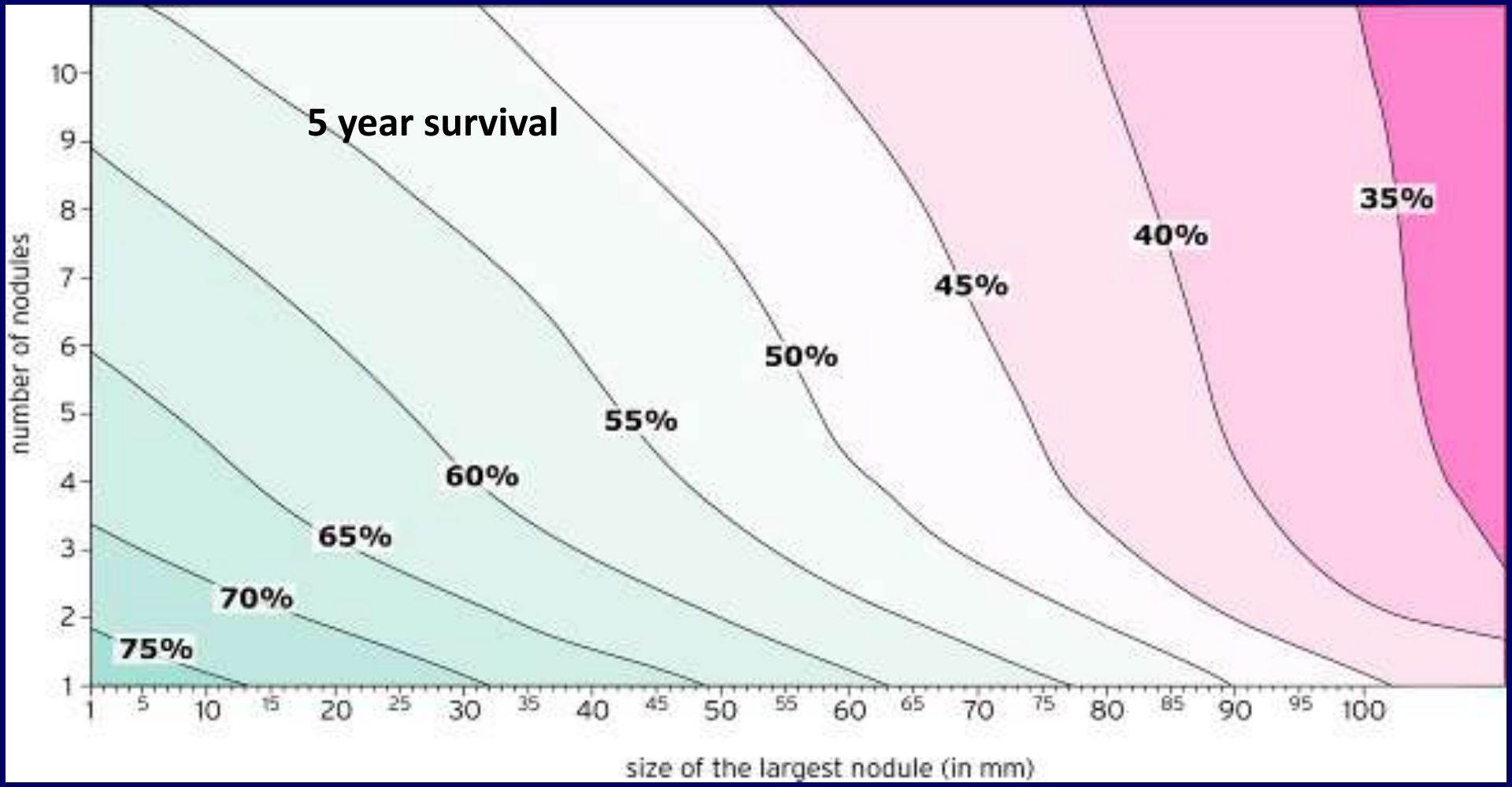


Liver transplant and HCC: maximum size and number of nodules (Adam 2003)



PREDICTING SURVIVAL AFTER LT IN PATIENTS WITH HCC
(Mazzaferro 2008)

Contour plot according to Size and Number of HCC nodules

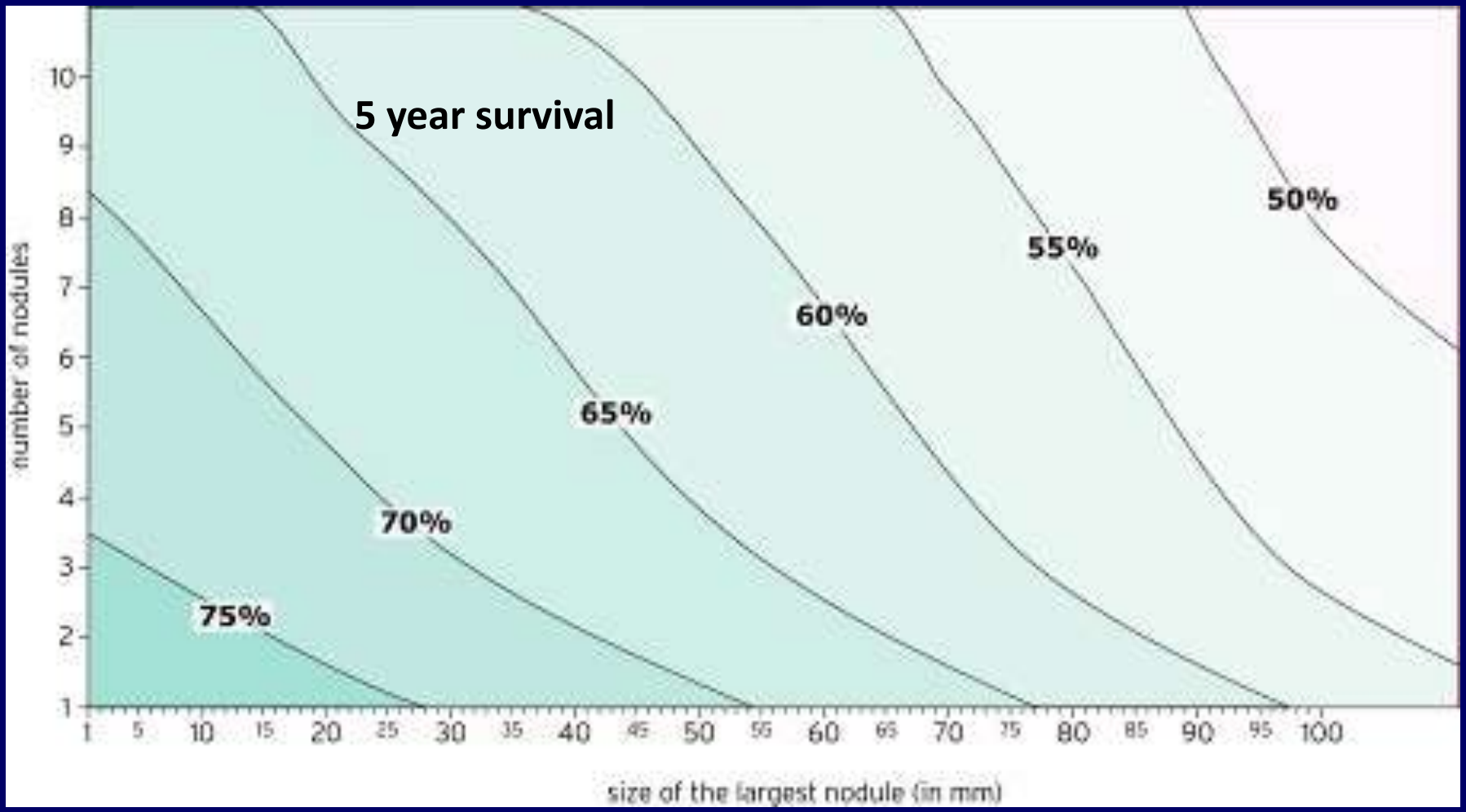


PREDICTING SURVIVAL AFTER LT IN PATIENTS WITH HCC

(Mazzaferro 2008)

Contour plot according to Size and Number of HCC nodules

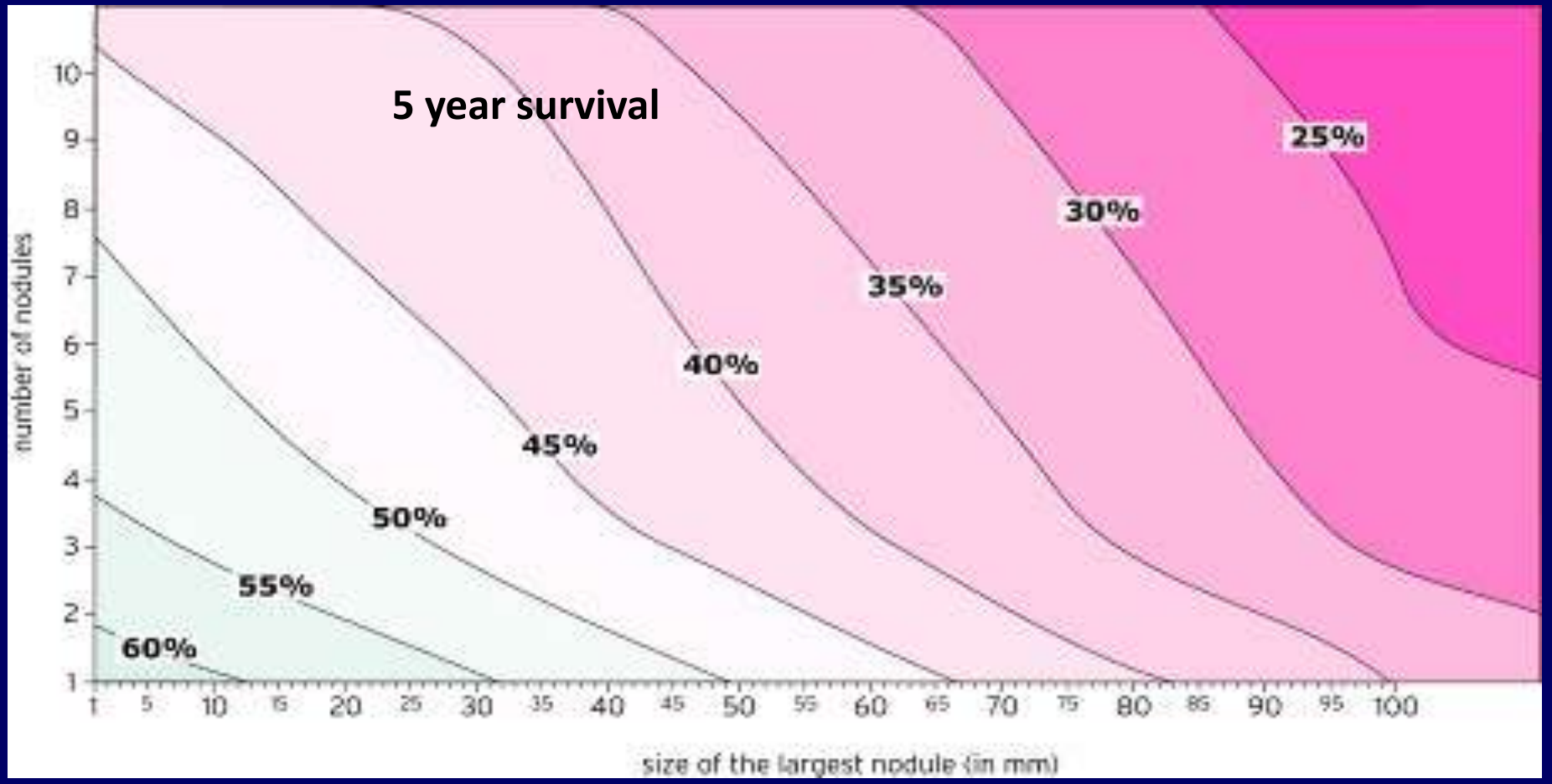
- Microvascular invasion absent -



PREDICTING SURVIVAL AFTER LT IN PATIENTS WITH HCC

(Mazzaferro 2008)

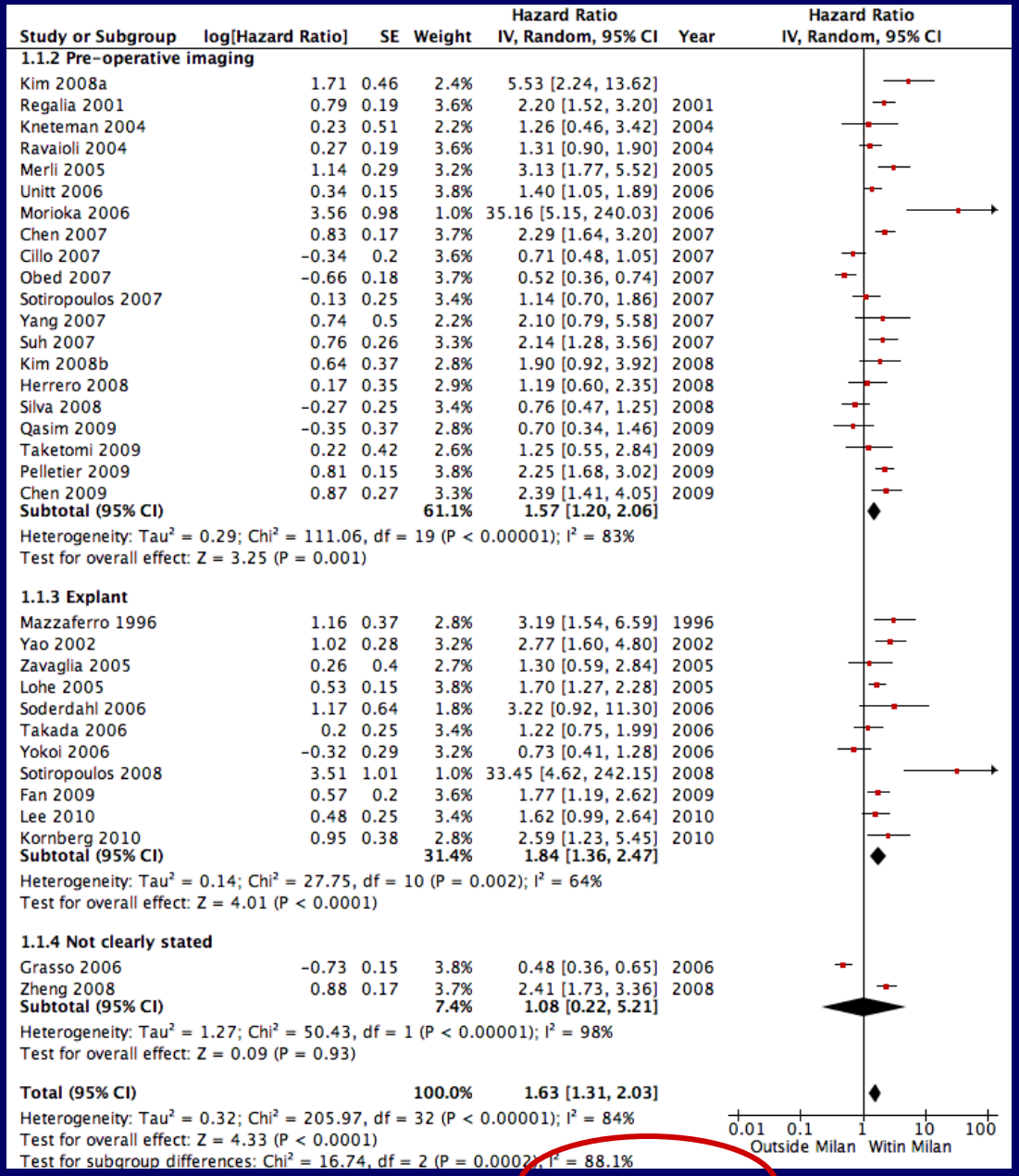
Contour plot according to Size and Number of HCC nodules
- Microvascular invasion present -



Meta-analysis of staging selection criteria for liver transplantation (Germani 2010)

	Overall survival	Disease-free survival	Recurrence
Beyond Milan criteria	⬇ 1.6x	⬇ 3.2x	⬆ 2.8x
Beyond UCSF criteria	⬇ 1.7x	⬇ 3.4x	⬆ 6.1x
TNM stage III-IV	⬇ 1.5x	-	-
Total tumour diameter ≥10cm	⬇ 4.5x	-	-
Total tumour diameter ≥9cm	-	⬇ 1.9	-
Diameter largest tumour >3cm	⬇ 1.5x	-	⬆ 6.6x
Tumour "size"* ≥ 5cm	⬇ 1.9x	⬇ 4.3x	⬆ 2.5x
Tumour number (cont. var.)	ns	-	ns
Multiple tumours	ns	-	-
Tumour number (≥3)	⬇ 1.2	ns	ns

** without other definition*



Meta-analysis of the studies comparing overall survival between patients outside and within Milan criteria

Germani 2010

Salvage liver transplantation after resection for HCC in cirrhotics

- 80% transplantable (Poon 2003)
- 20% transplantable (Adam 2003)

- More than one nodule poor prognosis resection

- Outcome can be similar to 1^{o} transplantation
  - recurrence 8-10% (Majno 1999)

Adjuvant and alternative therapy to liver transplantation

Therapies for Hepatocellular Carcinoma

- **Surgical resection**

- **Percutaneous therapies**

  Percutaneous ethanol injection (PEI)
  Radiofrequency ablation (RFA)
  Percutaneous acetic acid injection (PAI)
  Microwave ablation and others

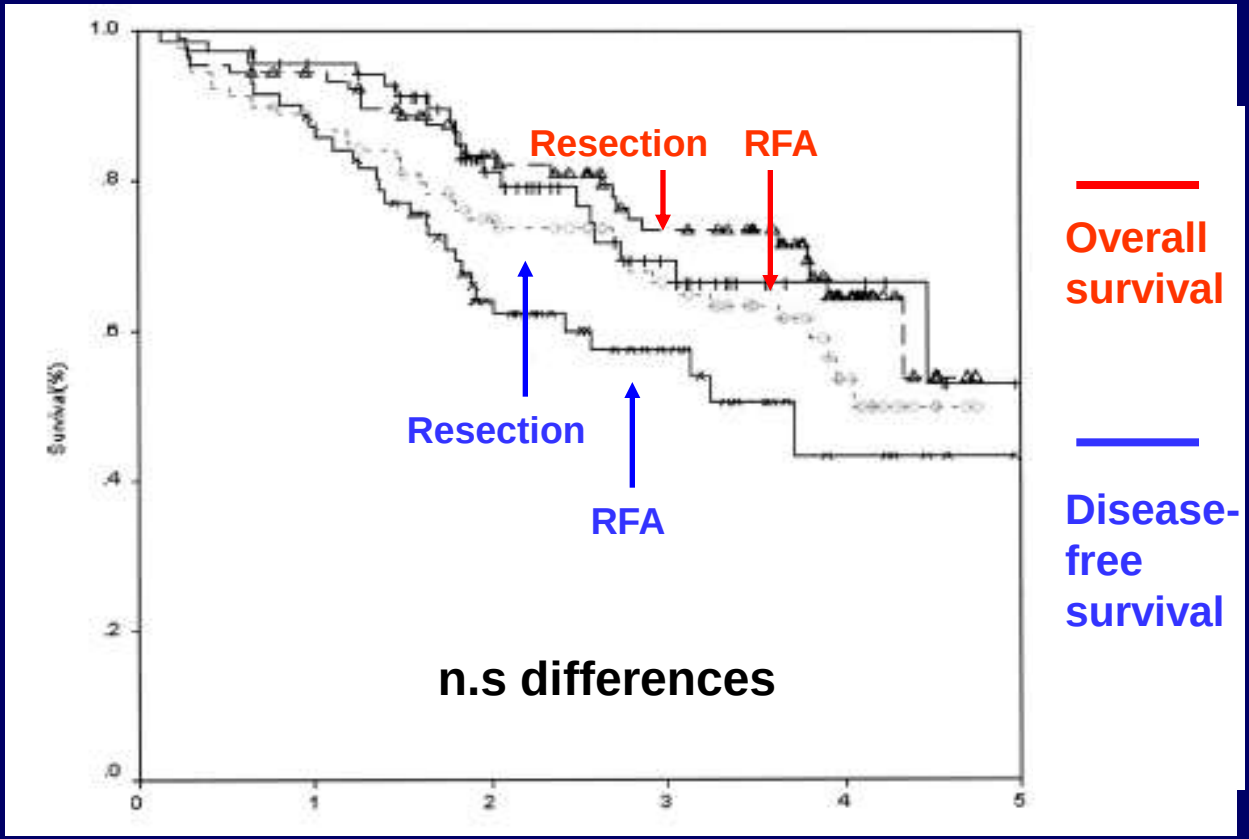
- **Transarterial therapies**

  Transarterial embolisation (TAE)
  Transarterial chemoembolisation (TACE)
  Drug eluting bead (DEB-TACE)
  Transarterial radionuclide embolisation (TARE)
  Transarterial oil chemoembolisation (TOCE)

- **Sorafenib**

RFA vs SURGICAL RESECTION

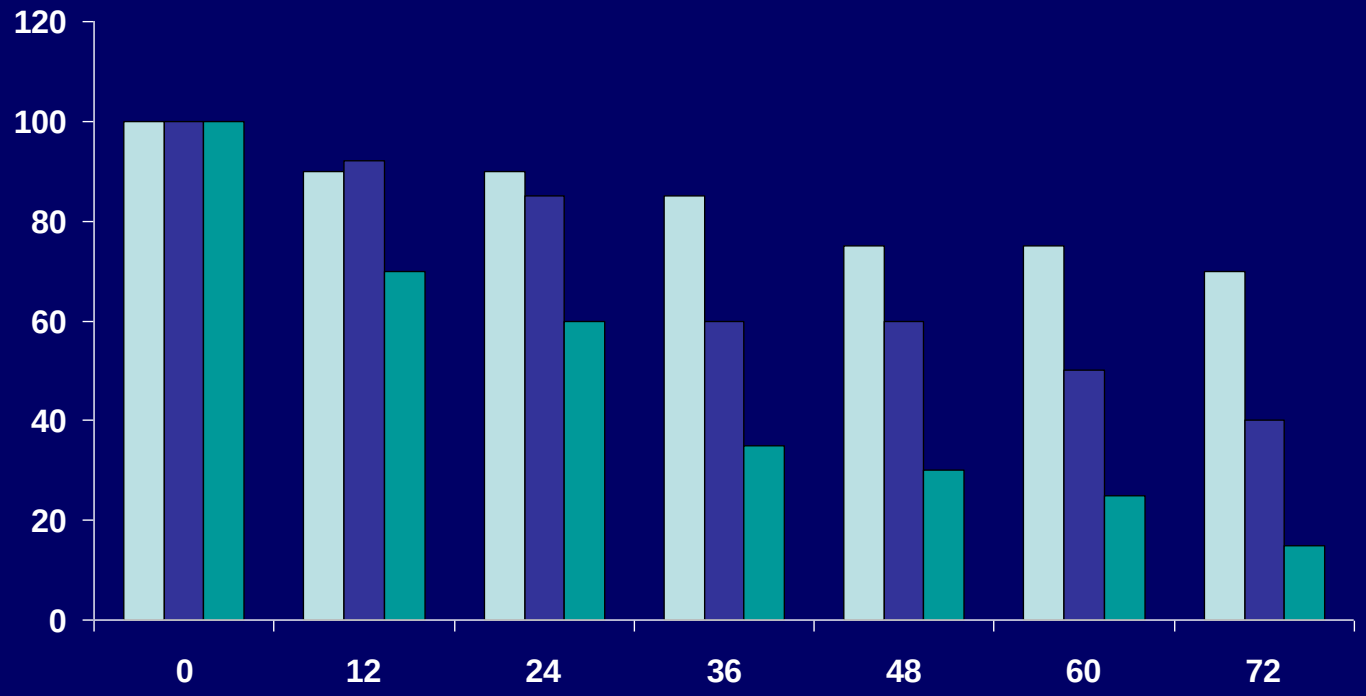
RCT: 180 patients with solitary HCC ≤ 5cm



Chen 2006

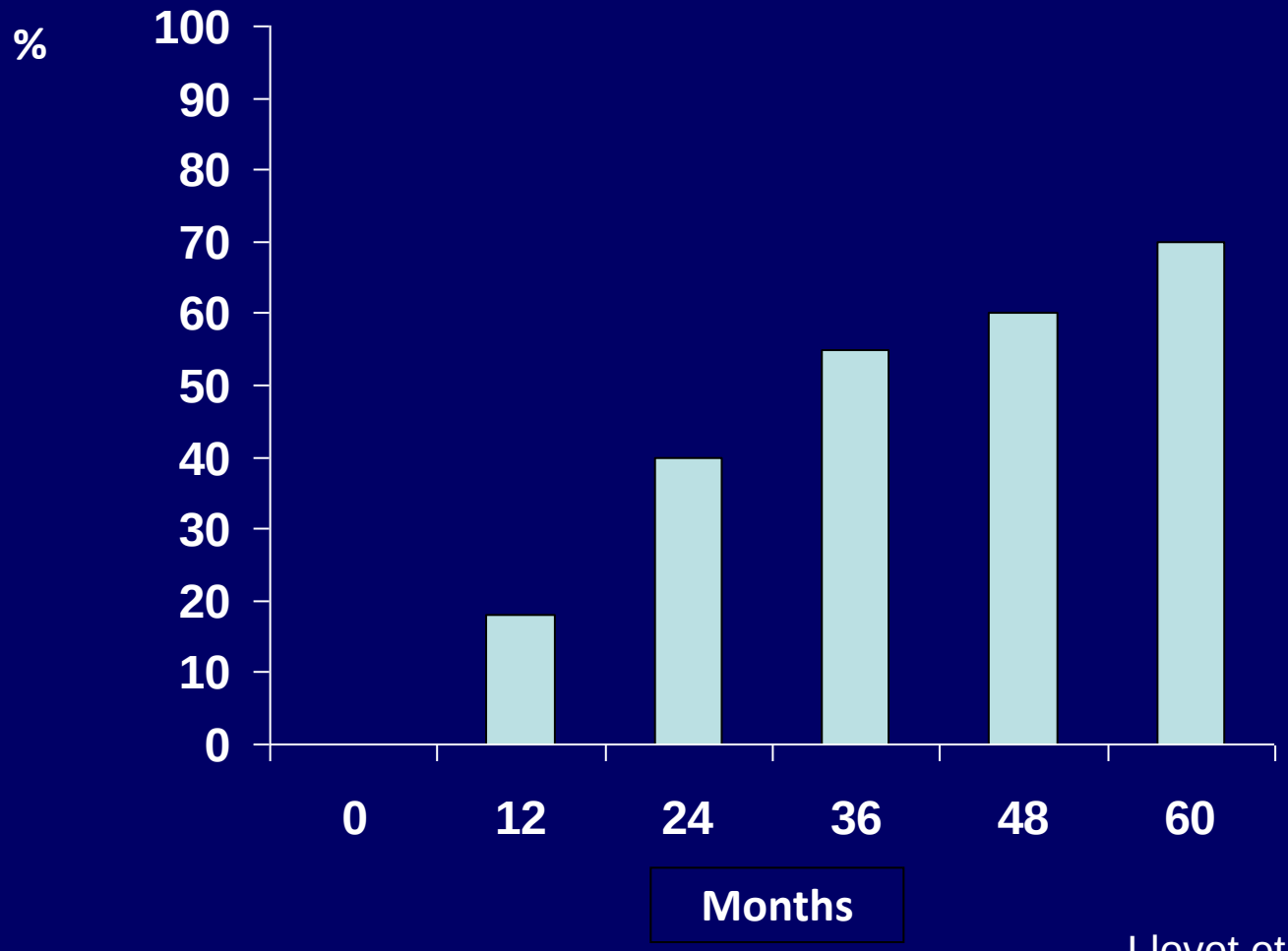
Survival following resection of HCC in cirrhosis

Llovet et al Hepatology 1999



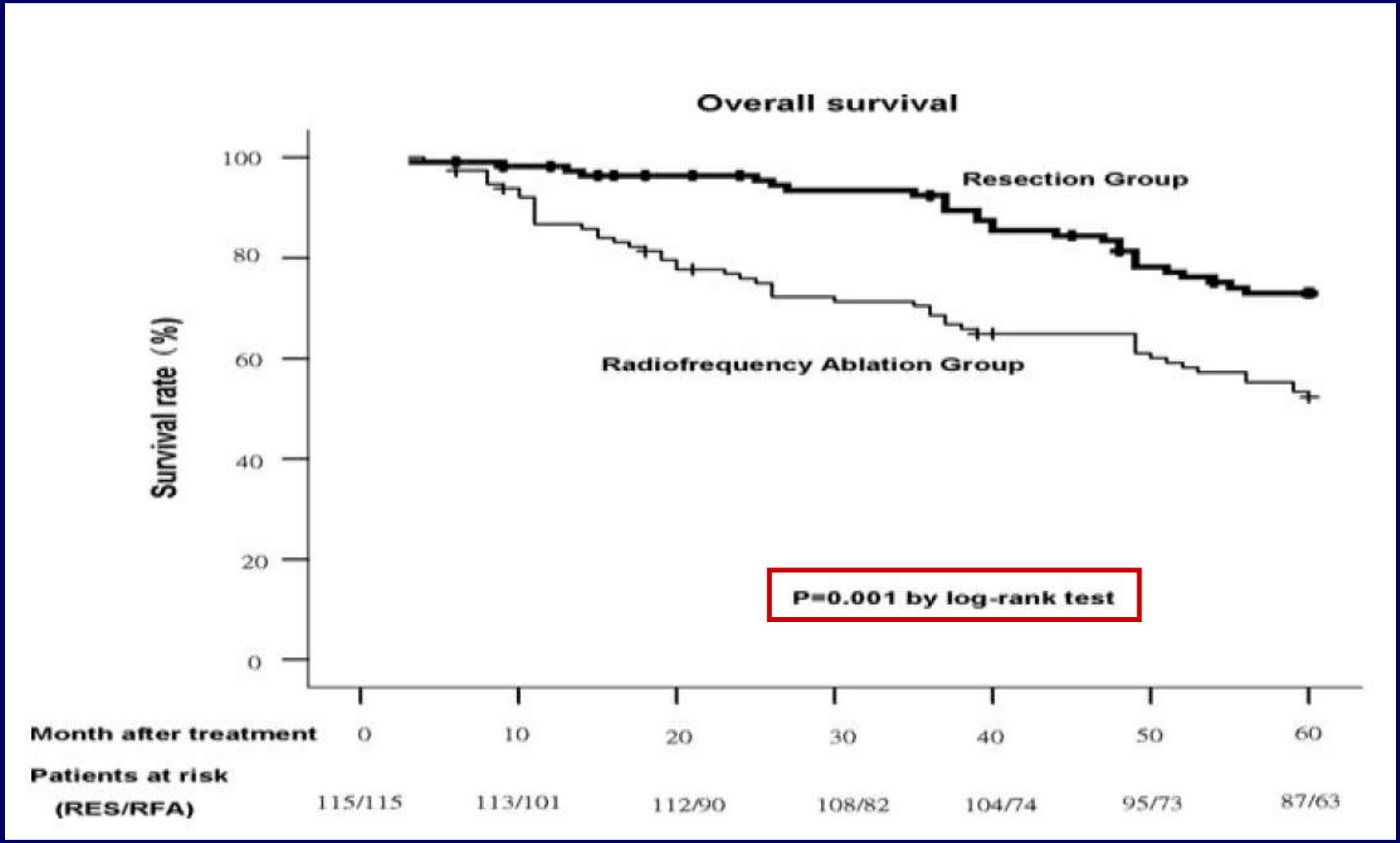
A	No portal hypertension HVPG < 10mmHg	5 yr survival 74%
B	Portal hypertension, normal serum Bilirubin	5yr survival 50%
C	Portal hypertension and raised Bilirubin	5yr survival 25%

Probability of recurrence after surgery for HCC



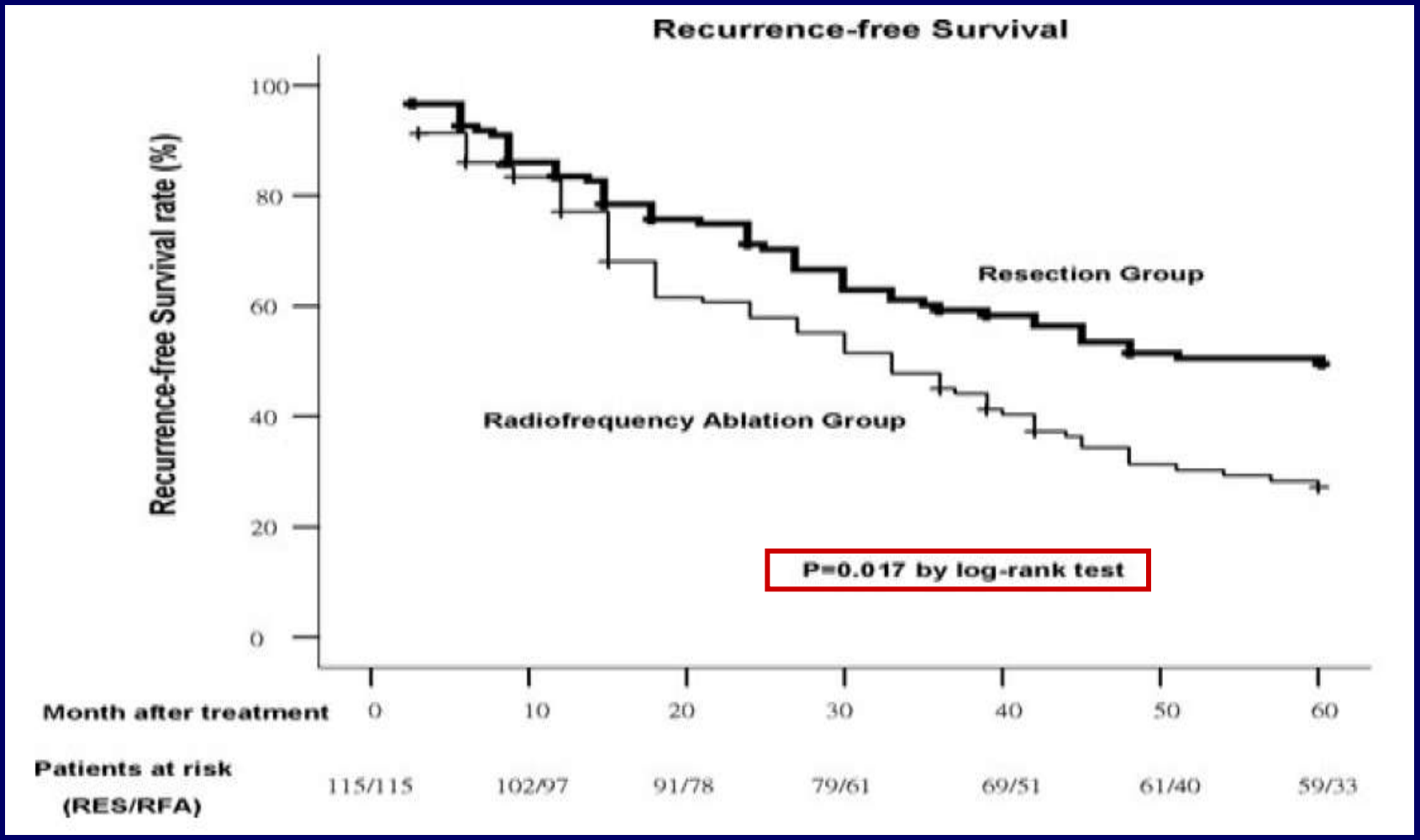
Llovet et al Hepatology 1999

A RCT Comparing RFA and Surgical Resection for HCC Conforming to the Milan Criteria



Huang 2010

A RCT Comparing RFA and Surgical Resection for HCC Conforming to the Milan Criteria



Huang 2010

Salvage liver transplantation after resection for HCC in cirrhotics

- 8 pathological high risk offered LT (Sala 2004)
  - 2 refused
  - 6 OLT (5 other tumour foci)
    - 1 early recurrence
    - 4 tumour free-median f.u. 4 y

- Intention to treat analysis
  - if can transplant this is better (Adam 2003)

Adjuvant Therapy for HCC before LT

Shortage of donors

↓

Increased waiting list

↓

Tumour progression while waiting on list

↓

Increased drop-out rate

(up to 20-50% if the waiting time exceeds 12 months)

Prioritization schedules affect this time-line

Adjuvant Therapy for HCC before LT

AIMS:

- To control tumour growth while patient awaits an organ

- To cause significant tumour necrosis,

  which may reduce tumor dissemination during surgery

Adjuvant Therapy for HCC before LT

Aimed to Downstage?

Biological plausibility?

No evidence

Cost-Effectiveness of Adjuvant Therapy for Small HCCs During the Waiting List for LT

By statistical modelling

Ablation of small tumours with PEI, RFA, TAE, TACE is cost-effective if the expected waiting time is longer than 6 months
PEI increased life expectancy from 5.2 to 6.7 months
at a cost of $20000/y of life gained (cost-effective)

but

TACE may induce liver failure and death in patients with decompensated disease.

Seeding of tumor cells may occur following PEI and RFA

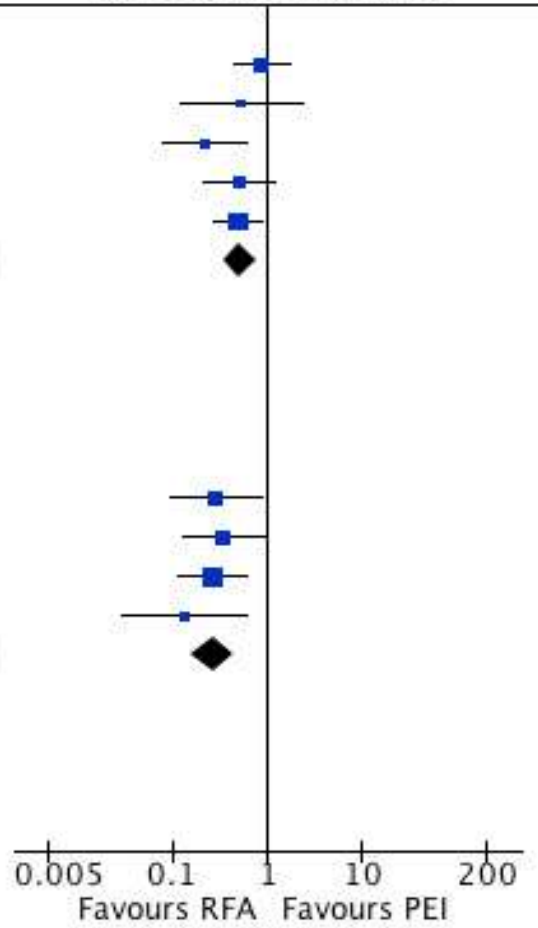
Llovet JM et al Gut 2002;50:123-128

RADIOFREQUENCY ABLATION

- Radiofrequency thermal energy applied to the tumor to generate coagulative necrosis
- First-line therapy for unresectable HCC in many centres
- Best outcomes: Child-Pugh A or B + HCC < 4cm
- 3 and 5-y survival = 78% and 54%
- Major complications: 2-9%

Meta-analysis of the studies comparing proportion dead, and local recurrence between radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) for hepatocellular carcinoma

Study	RFA Events	RFA Total	PEI Events	PEI Total	Weight	Odds Ratio M-H, Random, 95% CI
Proportion dead						
Brunello 2008	26	70	28	69	26.7%	0.87 [0.44, 1.71]
Lencioni 2003	3	54	5	50	7.6%	0.53 [0.12, 2.34]
Lin 2004	6	52	19	52	14.6%	0.23 [0.08, 0.63]
Lin 2005	10	62	17	62	18.6%	0.51 [0.21, 1.22]
Shiina 2005	25	118	40	114	32.5%	0.50 [0.28, 0.89]
Subtotal (95% CI)		**356**		**347**	**100.0%**	**0.52 [0.35, 0.78]**
Total events	70		109			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.70$, df = 4 (P = 0.32); $I^2 = 15\%$						
Test for overall effect: Z = 3.17 (P = 0.001)						
Local recurrence						
Lencioni 2003	5	54	13	50	22.9%	0.29 [0.10, 0.89]
Lin 2004	7	52	16	52	27.9%	0.35 [0.13, 0.94]
Lin 2005	10	62	26	62	35.9%	0.27 [0.11, 0.62]
Shiina 2005	2	118	13	114	13.4%	0.13 [0.03, 0.61]
Subtotal (95% CI)		**286**		**278**	**100.0%**	**0.27 [0.16, 0.45]**
Total events	24		68			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.12$, df = 3 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 4.91 (P < 0.00001)						



No statistical difference if tumour ≤ 2 cm

Germani et al. J Hepatol 2010

RFA before liver transplantation

	Mazzaferro 2004	Lu 2005
Patients	50	52
Morbidity	8%	-
Transplanted	100%	94%
Mean wt	9.5m	12.5m
Survival 3yr	83%	76%
Recurrence	4%	0%
Necrosis explant	55%	85%

SEEDING FOLLOWING LIVER BIOPSY / LOCOREGIONAL THERAPY

Cohorts with total number biopsies stated

SEEDING	median risk	
- Biopsy alone	2.28%	(0-11%)
- PEI and biopsy	1.4%	(1.15-1.85%)
- RFA NO biopsy	0.61%	(0-5.56%)
- RFA and biopsy	0.72%	(0-10%)

NB HCC higher risk of seeding than other tumours

Pancreatic (0.003-0.017%)

Probably under-reported

(Stigliano 2007)

TRANSARTERIAL EMBOLISATION

Criteria

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

TRANSARTERIAL EMBOLIZATION Variables

- Particles
  - Gel foam
  - PVA
  - microspheres
- Chemotherapy
  - none
  - Cisplatin
  - Doxorubicin
  - Mitomycin C
  - 5FU
- Extent of embolisation
  - Lobar
  - Segmental
  - Subsegmental
- Frequency
  - Fixed
  - PRN

Marelli 2007

EMBOLISING AGENTS AND TRANSARTERIAL THERAPY
(Pleguezuelo 2008)

TRANSIENT ARTERIAL OCCLUSION

- **Gelatin sponge:**
  - **particles, pellets, powder, fragments, strips** *(Lo 2002, Llovet 2002)*
  - **last 2 weeks** *(Coldwell 1994; Chung 1998)*
- **DSM (Degradable starch microspheres): 80min occlusion** *(Dakhil 1982)*
- **Autologous blood clot** *(Gunji 2002)*

EMBOLISING AGENTS AND TRANSARTERIAL THERAPY
(Pleguezuelo 2008)

PERMANENT ARTERIAL OCCLUSION

- **PVA particles (50-250µm diameter)**

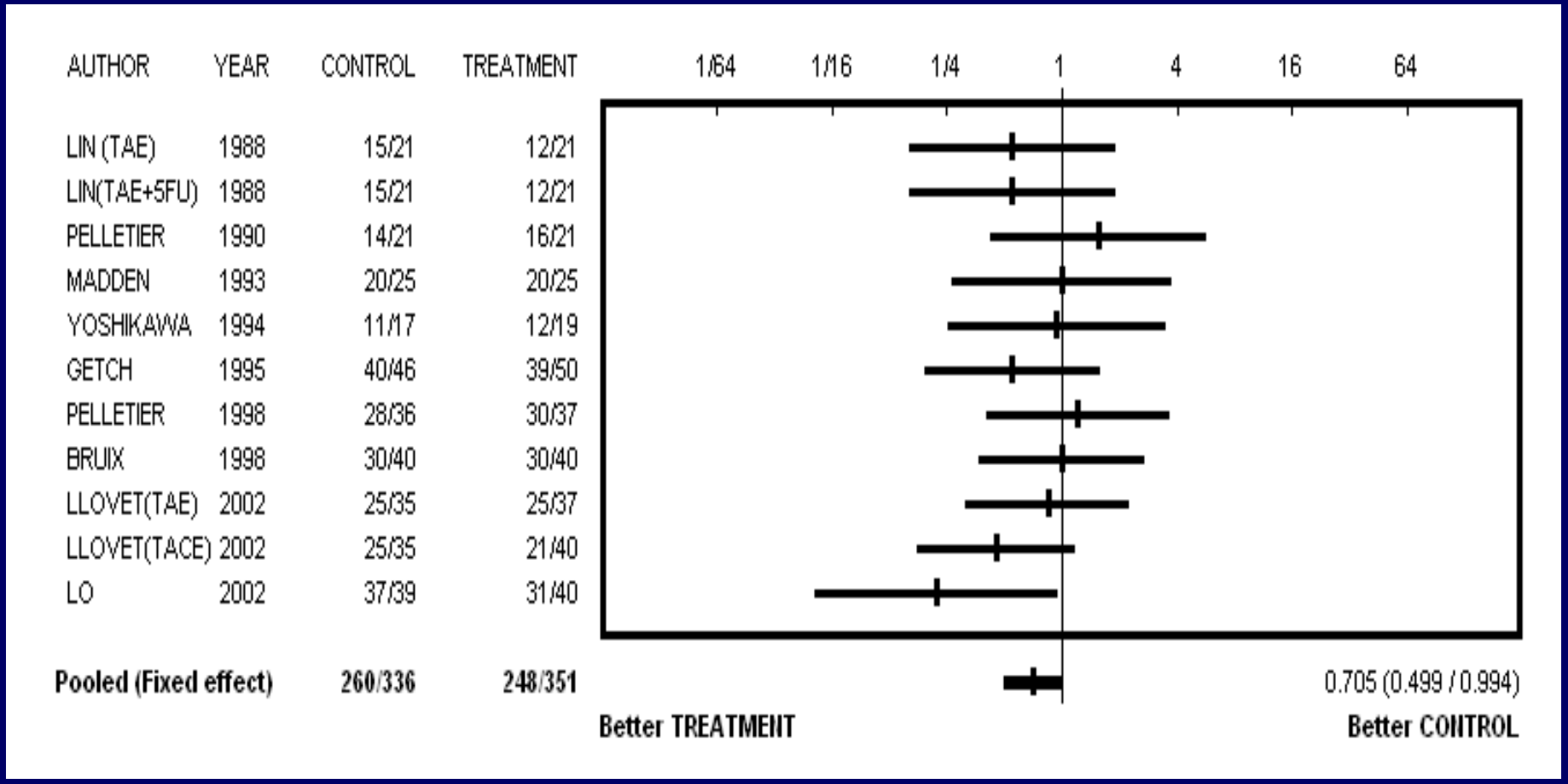
  No difference vs. Gelfoam *(Brown 2005)*

- **DEB (drug eluting beads) (100-300 and 300-500 µm diameter)**
  Loaded with doxorubicin *(Varela 2007)*

- **EMBS (embospheres) (100-300 µm diameter)**

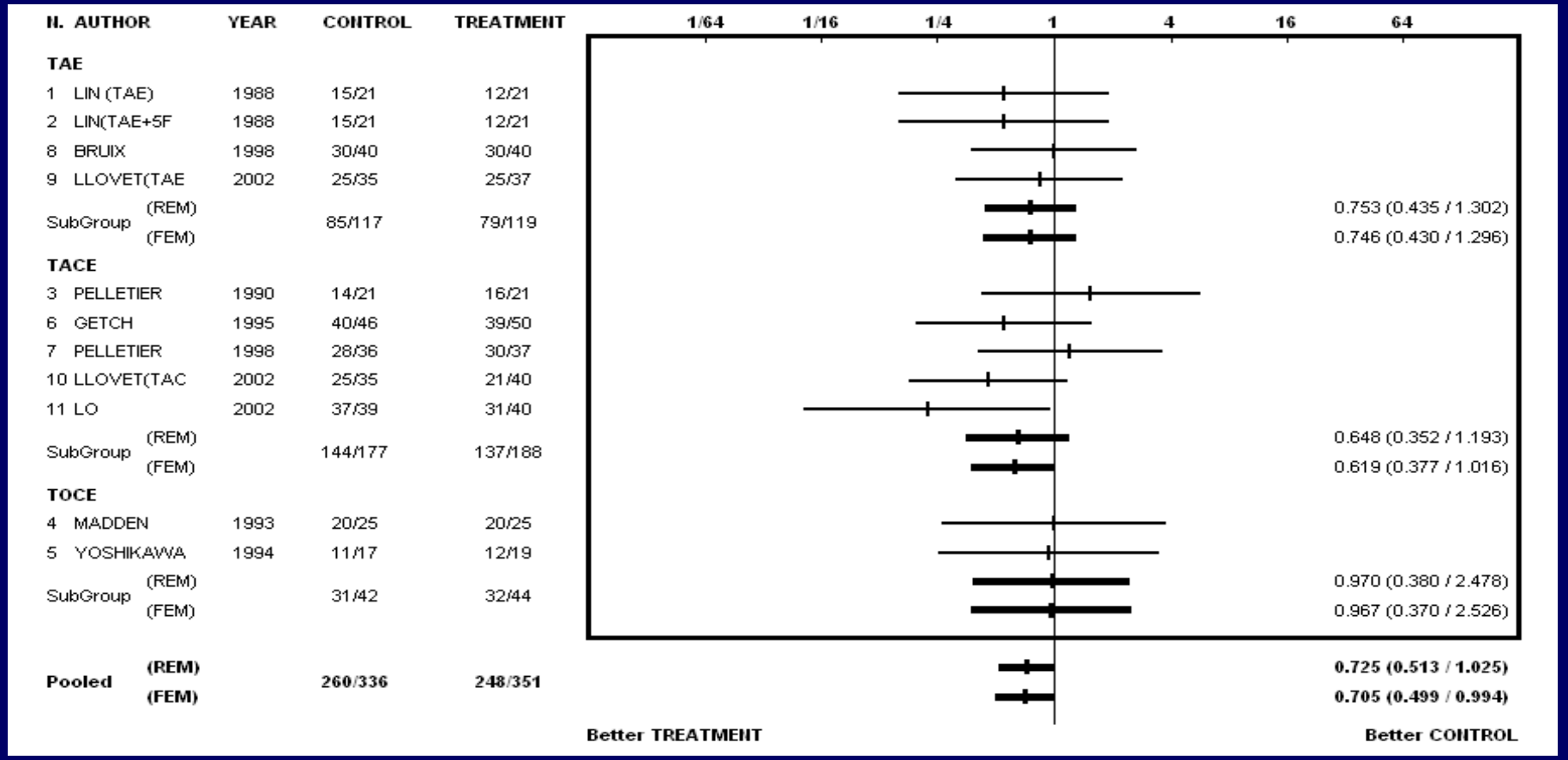
  More deformable *(Amesur 2008)*

TRANSARTERIAL EMBOLIZATION vs CONTROLS



Marelli 2007

TACE / TAE / TOCE vs CONTROLS



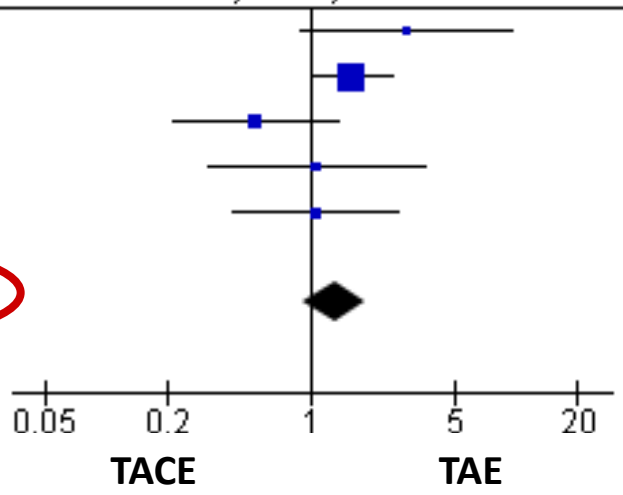
Marelli 2007

Survival outcomes following TACE or TAE in patients with HCC in the five existing RCTs to date

Study or Subgroup	TACE Events	TACE Total	TAE Events	TAE Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chang 1994	14	22	9	24	5.5%	2.92 [0.88, 9.67]
Kawai 1992	82	148	62	141	49.3%	1.58 [1.00, 2.52]
Llovet 2002	21	40	25	37	21.5%	0.53 [0.21, 1.34]
Malagari 2010	6	41	6	43	8.7%	1.06 [0.31, 3.59]
Meyer 2010	13	44	12	42	15.1%	1.05 [0.41, 2.66]
Total (95% CI)		**295**		**287**	**100.0%**	**1.30 [0.93, 1.84]**
Total events	136		114			

Heterogeneity: Chi² = 6.34, df = 4 (P = 0.17); I² = 37%

Test for overall effect: Z = 1.52 (P = 0.13)



Tsochatzis 2011

TRANSARTERIAL EMBOLIZATION
Toxicity

- Post embolisation syndrome 60-80%
- Liver failure 7.5% (range 0-48%)
- Abscess 1.8%
- Bile duct injury 2%
- Upper GI bleeding 3%
- Irreversible renal dysfunction 2.8%
- **30 day mortality 2.4%**

Marelli 2007

TACE BEFORE LT- SYSTEMATIC REVIEW

- 5 comparative studies (1600 patients)

- 5 cohort studies (197 patients)

- 4 comparative studies with HCC meeting Milan criteria, showed no significant difference in either disease-free survival or overall survival between TACE before OLT (n=193) vs OLT alone (n = 206)

Marelli, 2006

TACE BEFORE LT - COMPLICATIONS

- Complication rate: 27%

- Fever and abdominal pain are the most common

- Risk of liver failure related to pretreatment liver function (Child C: 60%)

- Related mortality up to 4%

- Not appropriate in decompensated cirrhosis

Lo 2002; Llovet 2002; Poon 2000

TACE AS A BRIDGE TO LT FOR HCC: An evidence-based analysis

- 12 studies (4 comparative; 8 non-comparative)

- Pre-LT TACE does not improve long-term survival

- There is no convincing evidence that TACE allows expansion of current selection criteria for LT, nor that TACE decreases drop-out rates on the waiting list

- TACE does not increase the risk of postoperative complications

- There is insufficient evidence that TACE offers an benefit when used prior to LT, neither for early nor for advanced HCC

Lesurtel, 2006

EFFICACY OF TACE BEFORE LT – SYSTEMATIC REVIEW

Complete tumour necrosis was achieved in a median of 15% of treated nodules (range 0-28%)

Tumour necrosis > 50% was achieved in a median of 60% of nodules (21-100%)

No study reported correlation between the amount of tumour necrosis and the recurrence rate

Marelli, 2006

INTERVAL OF EFFICACY FOR TACE FOR HCC WHILE IN WAITING LIST

- Decision analysis to simulate a RCT of TACE vs no TACE in 600 virtual patients with HCC and cirrhosis

-TACE had statistical benefit at waitlist time breakpoints of 4 and 9 months ($p < 0.05$)

· Time < 4m: Waitlist attrition similar (20 vs 38%; p=0.08)

· Time > 9m: Drop-out rates similar (33% vs 46%; p=0.06)

-TACE may be limited to patients transplanted between 4 to 9 months from first TACE.

Aloia, 2007

DRUG ELUTING BEADS (DEB)

- Beads (100-300 and 500-700 μm)

- Beads are entrapped in the neoplastic vascular bed and cytotoxic drug is released locally:

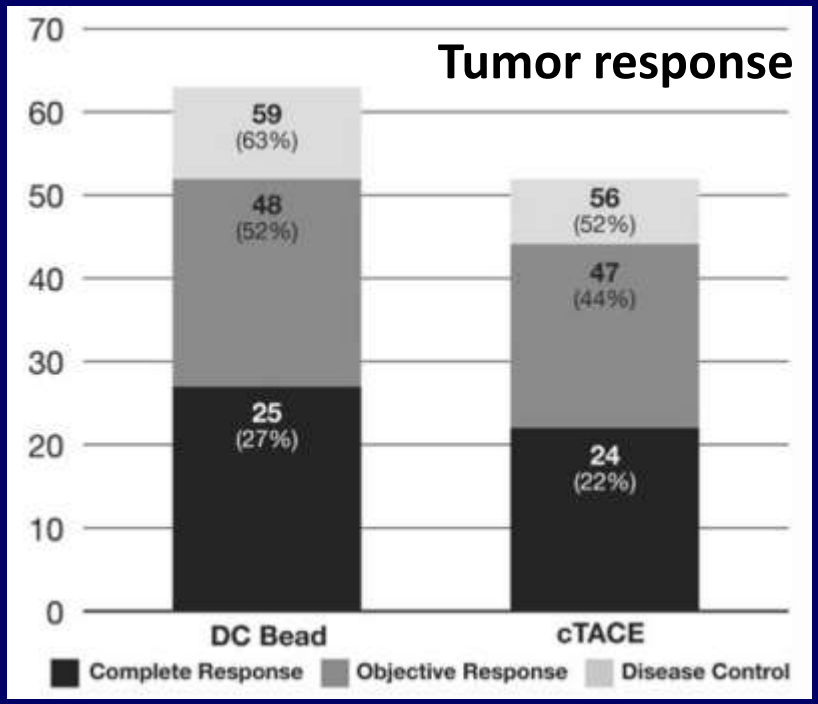
  · Sustained release (2 weeks)

  · Higher tumour concentration

  · Lower plasma concentration

Hong 2006

Randomized study of doxorubicin-eluting-bead embolization v. TACE for HCC: PRECISION V Study



No difference in survival

- **Increase in objective response in Child B, ECOG 1, bilobar disease and recurrent disease patients**

- **DC Bead associated with**
  - **improved tolerability (p<0.001)**
  - **lower rate of doxorubicin-related side effects (p=0.0001)**

(Lammer 2010)

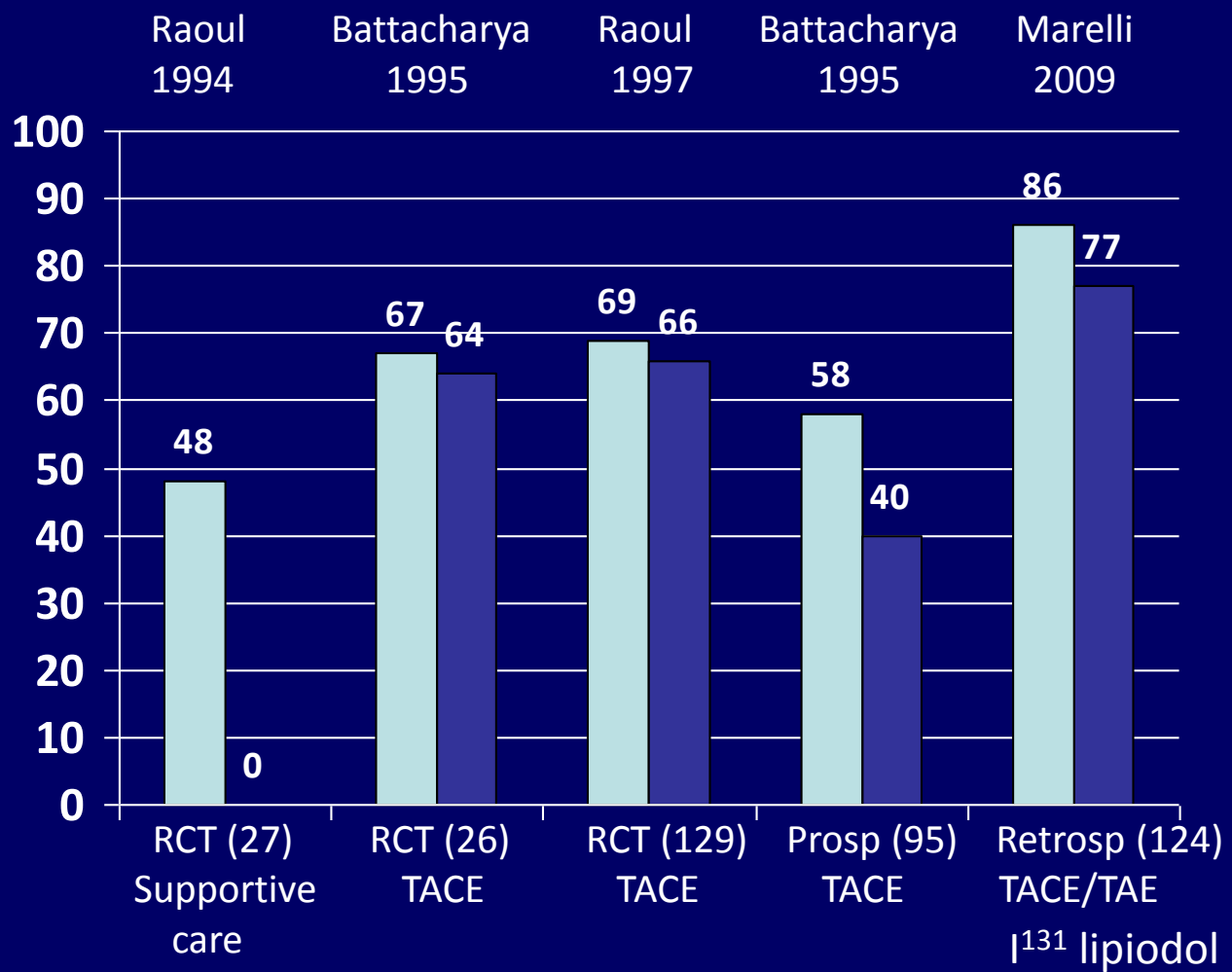
Safety Profile of Sequential Transcatheter Chemoembolization with DC Beads for HCC

- 237 pts treated with sequential DEBDOX with doxorubicin
- 30d mortality 1.26%
- Grade 5 complications 1.26%
- Grade 4 complications 5.48%
- Grade 2 liver function deterioration 4.2%
- Cholecystitis/grade 2 and 4 5.48%
- Post-embolization syndrome grade 1 or 2 86.5%
- Pleural effusion 3.37%
- Grade 1 procedure-related pancreatitis 0.45%
- grade 2 gastrointestinal bleeding 0.84%
- Procedure-associated skin erythema 0.84%

- No correlation of liver failure/liver function deterioration with bead diameter (100-300 vs 500-700 μm)

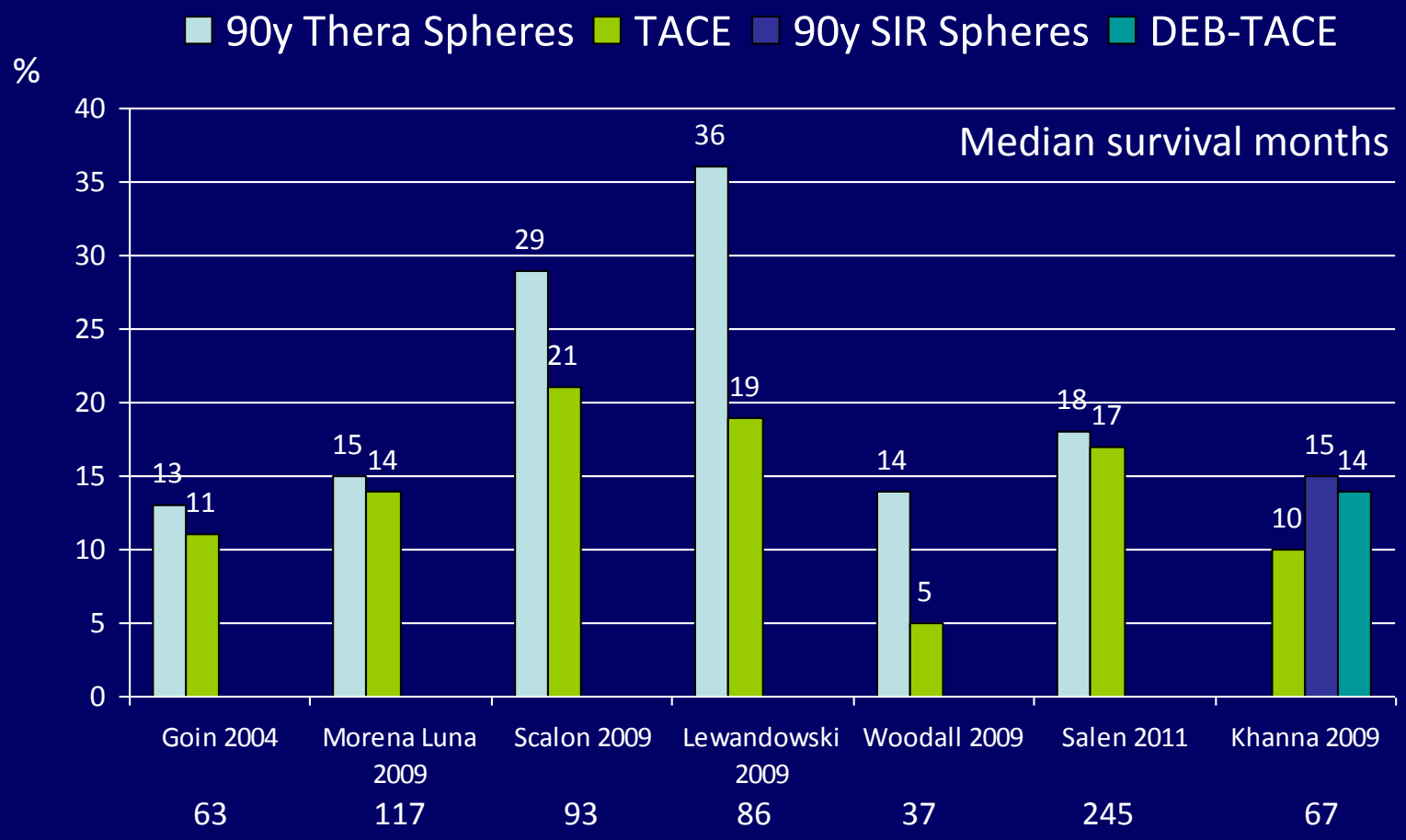
(Malgari 2010)

Survival of comparative studies of TARE I^{131} lipiodol first line therapy for unresectable HCC



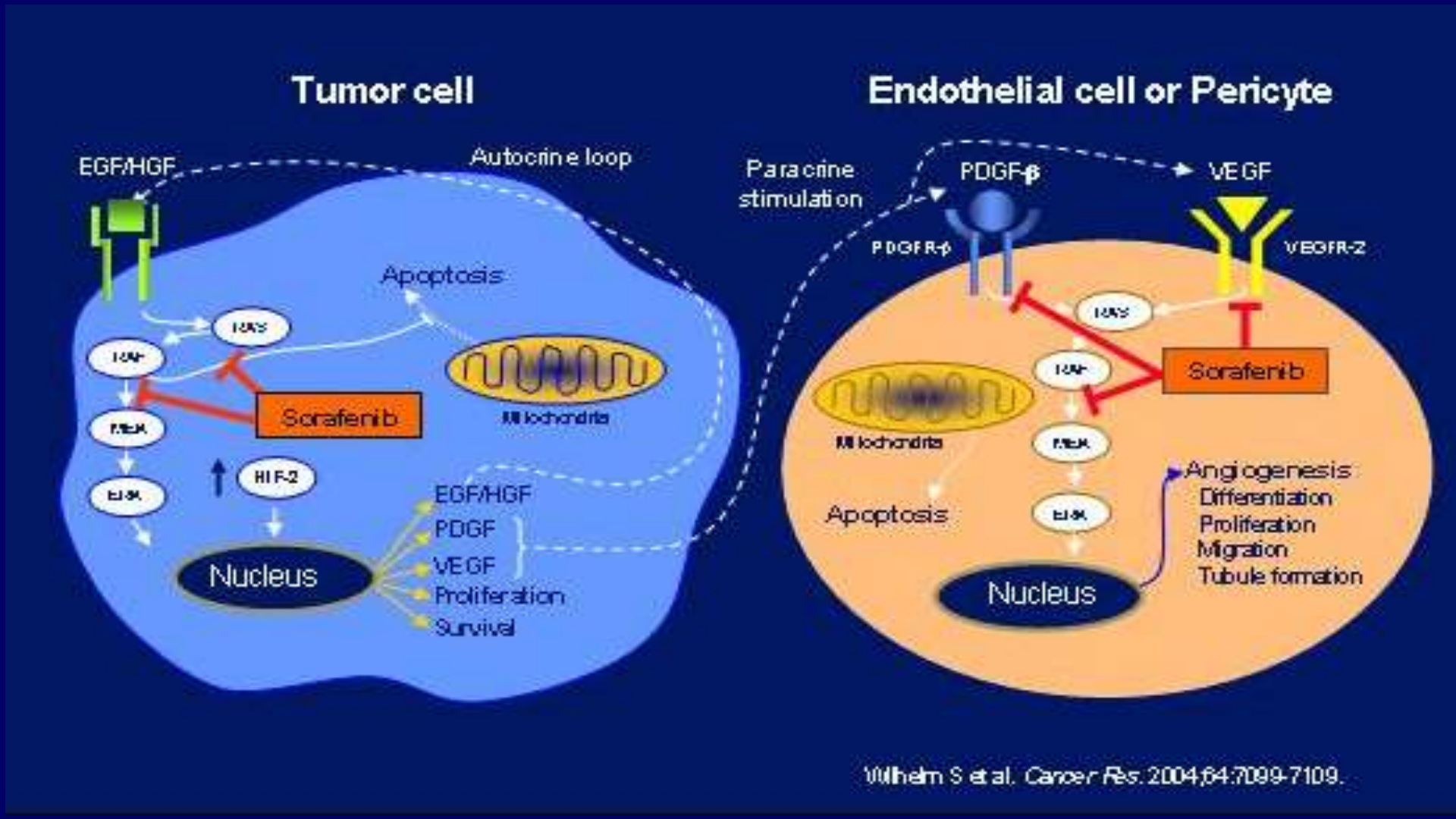
I^{131} lipiodol now withdrawn

Survival in comparative studies of 90Y microspheres TARE as first line therapy for unresectable HCC



Includes cirrhotics with PVT

SORAFENIB


Tumor cell
Endothelial cell or Pericyte
EGF/HGF
Autocrine loop
Paracrine stimulation
PDGF-β
VEGF
PDGFR-β
VEGFR-2
Apoptosis
Sorafenib
Mitochondria
HIF-2
EGF/HGF
PDGF
VEGF
Proliferation
Survival
Nucleus
Angiogenesis
Differentiation
Proliferation
Migration
Tubule formation
Wilhelm S et al. Cancer Res. 2004;64:7099-7109.

SORAFENIB
Rationale for Sorafenib

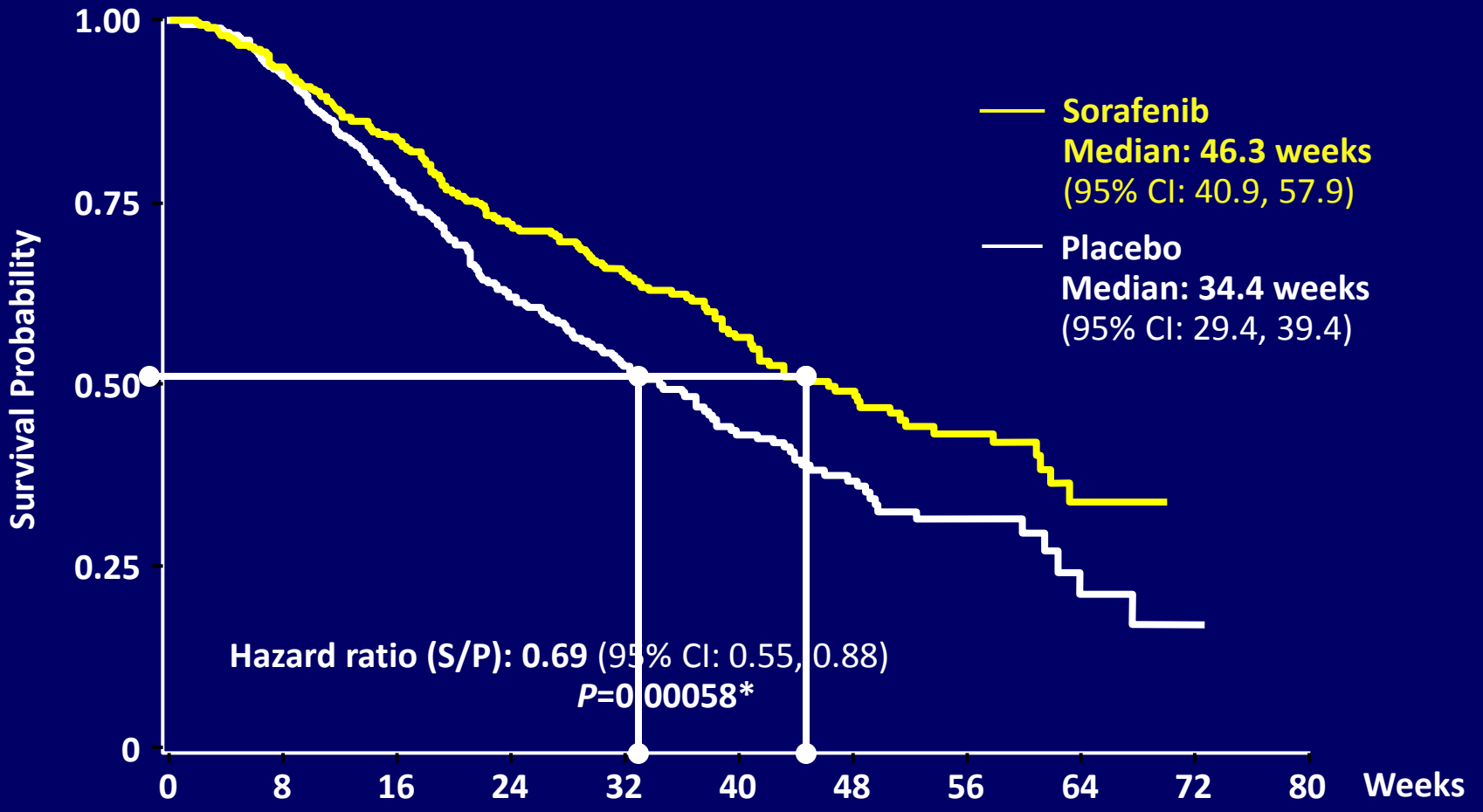
- VEGF and Raf kinase are overexpressed and activated in HCC
- RAF/MEK/ERK signalling pathway implicated in hepato-carcinogenesis
- Sorafenib is a multikinase inhibitor of Raf, VEGF, and other kinases.

SORAFENIB - SHARP study design

- International, multi-center Phase III
- Inclusion criteria
  - Histology-proven HCC
  - Advanced HCC
  - At least 1 measurable untreated lesion
  - ECOG 0-2
  - **Child-Pugh A**
  - No prior treatments
- Accrual 3/05-4/06
- Intention-to-Treat analysis

Llovet ASCO 2007

SORAFENIB - Phase III SHARP Trial
Overall survival (Intention-to-treat)

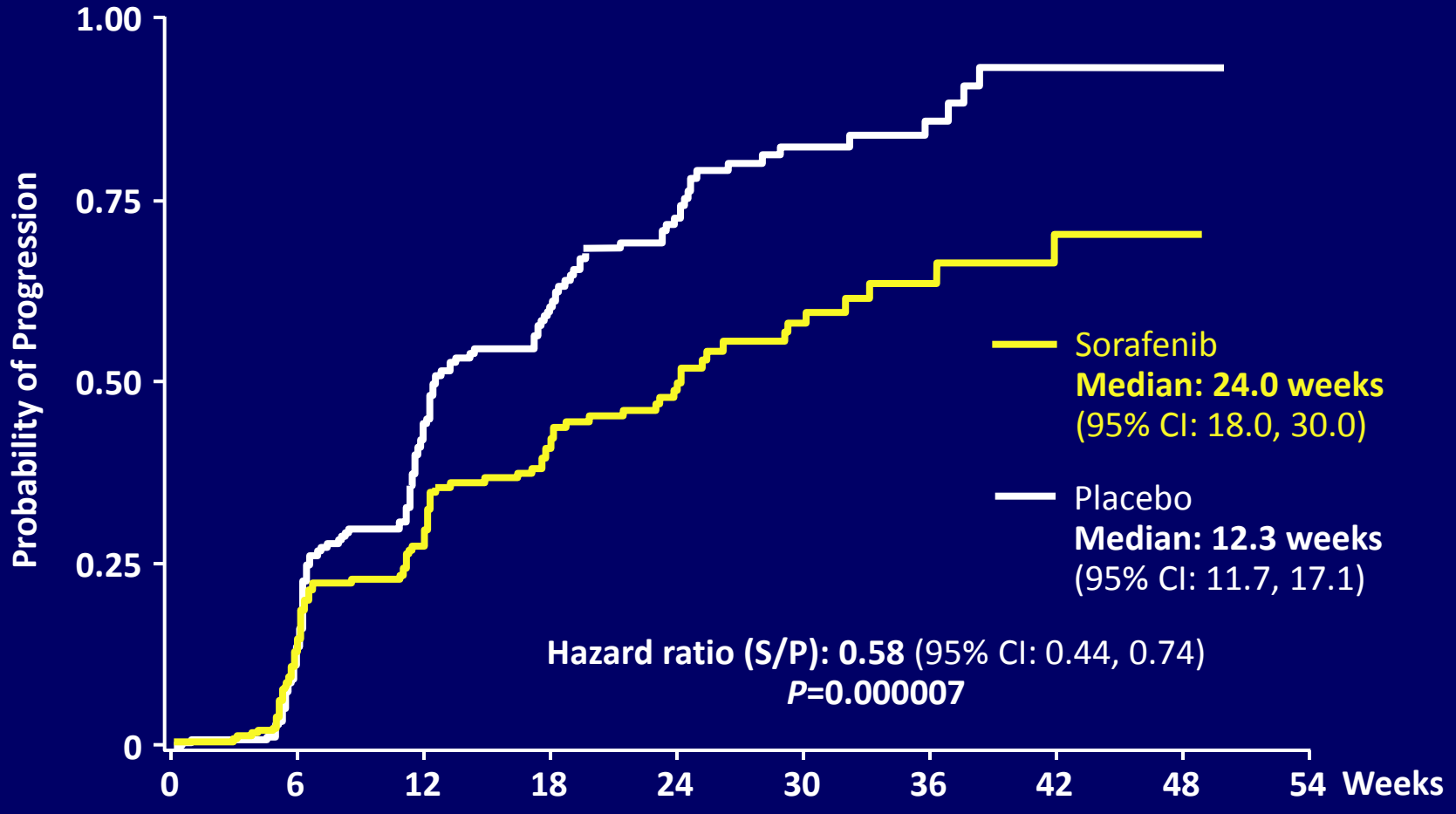


Patients at risk

Sorafenib:	299	274	241	205	161	108	67	38	12	0	0
Placebo:	303	276	224	179	126	78	47	25	7	2	0

Llovet ASCO 2007

SORAFENIB - Phase III SHARP Trial
Time to progression (Independent central review)



Patients at risk

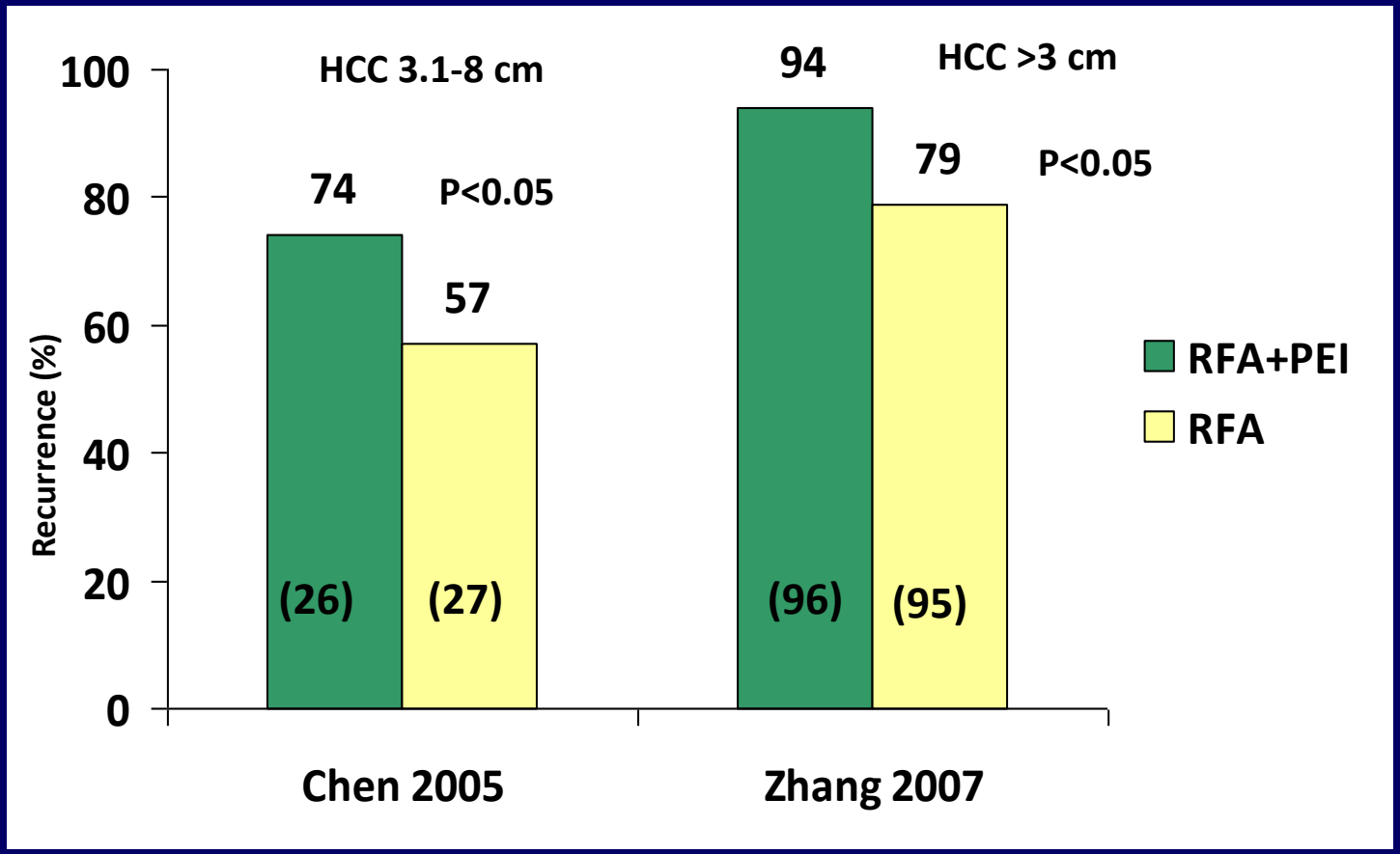
Sorafenib:	299	196	126	80	50	28	14	8	2	0
Placebo:	303	192	101	57	31	12	8	2	1	0

Llovet ASCO 2007

Potential future therapies

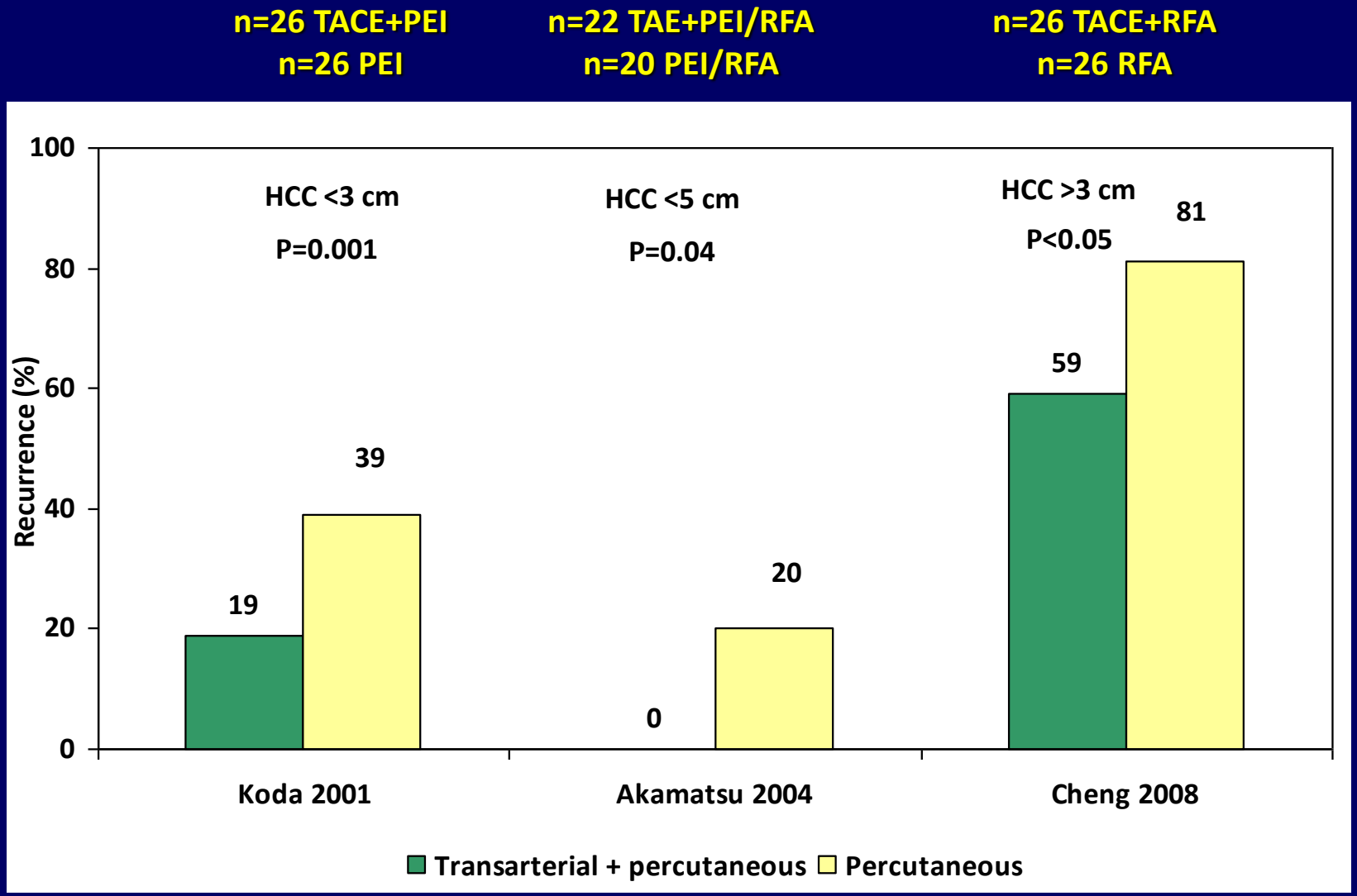
- Combined transarterial and percutaneous techniques
- Sorafenib and transarterial combinations
- New drugs - molecular profiling

THERAPY COMBINATIONS
TACE + PEI vs. TACE

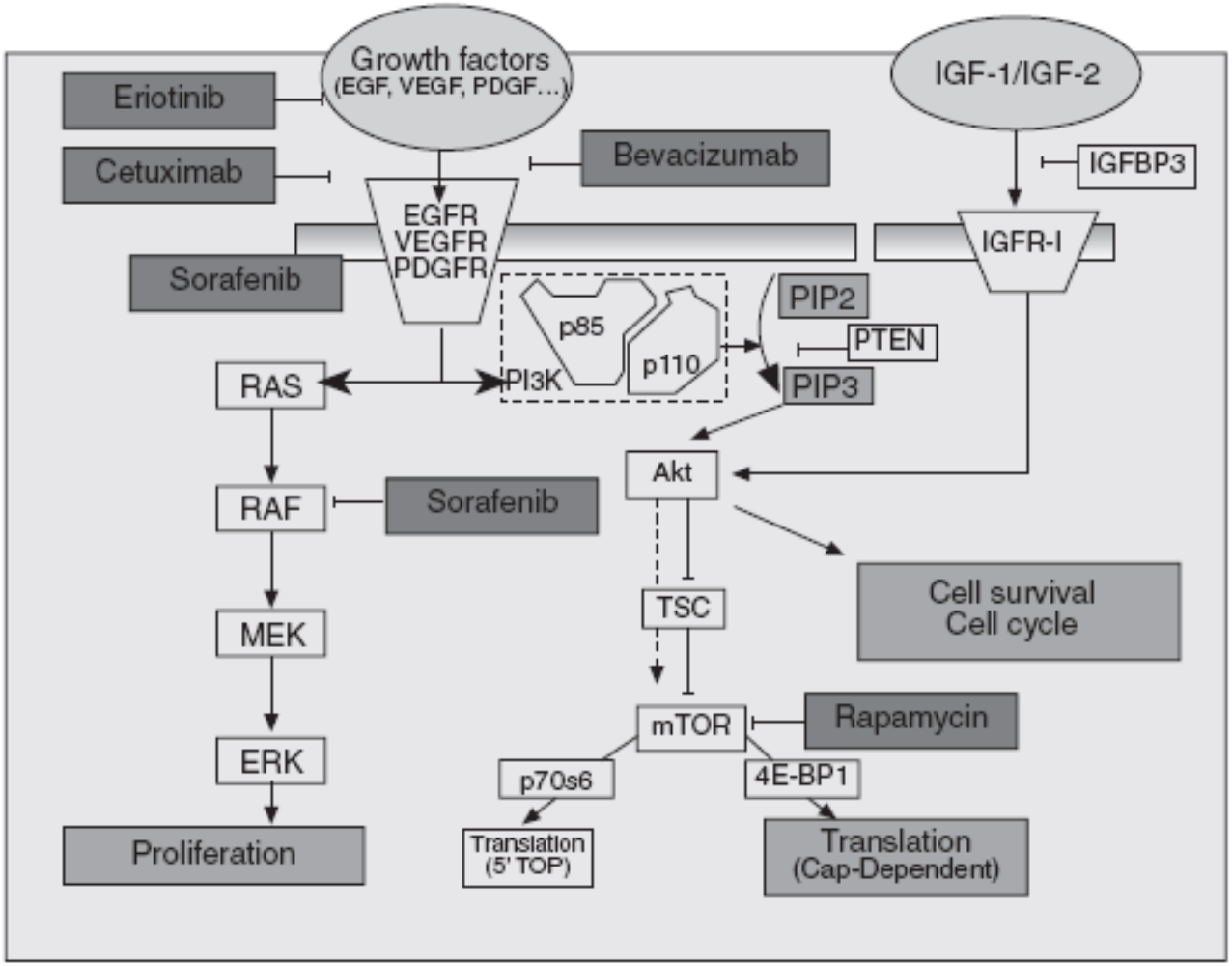


	TACE+PEI	TACE	
Complete necrosis (%)	85	52	p<0.05 *(Bartolozzi 1995)*
	55	5	p<0.05 *(Cheng 2008)*

THERAPY COMBINATIONS
TACE+PEI vs. RFA



MOLECULARLY TARGETED AGENTS



Targets and agents

EGFR:
TKI: Erlotinib, Lapatinig
Gefitinib
Ab: Cetuximab

VEGF:
TKI: Sorafenib
Ab: Bevacizumab

RAF:
TKI: Sorafenib

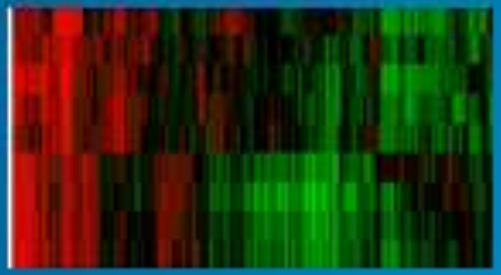
mTOR:
Rapamycin

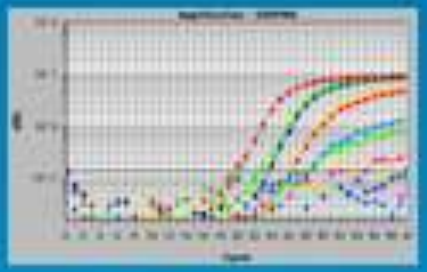
Proteasome inhibitors:
Bortezomib

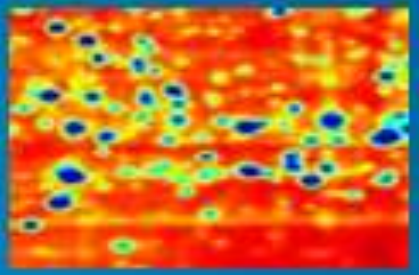
ClinicalTrials.gov

- FOLFOX4 vs Doxorubicin Phase III
- Doxorubicin+Bortezomib Phase II
- Oxaliplatin/Capecitabine/Cetuximab Phase II
- Dasatinib Phase II
- Sirolimu+Bevacizumab Phase I
- Sunitinib Phase II
- Gefitinib Phase II
- Bevacizumab Phase II
- Bevacizumab+Erlotinib Phase II
- Capecitabine Phase II
- Thalidomide Phase III
- Etoposide/Oxaliplatin/Capecitabine Phase II

Gene and Protein Expression Profiling



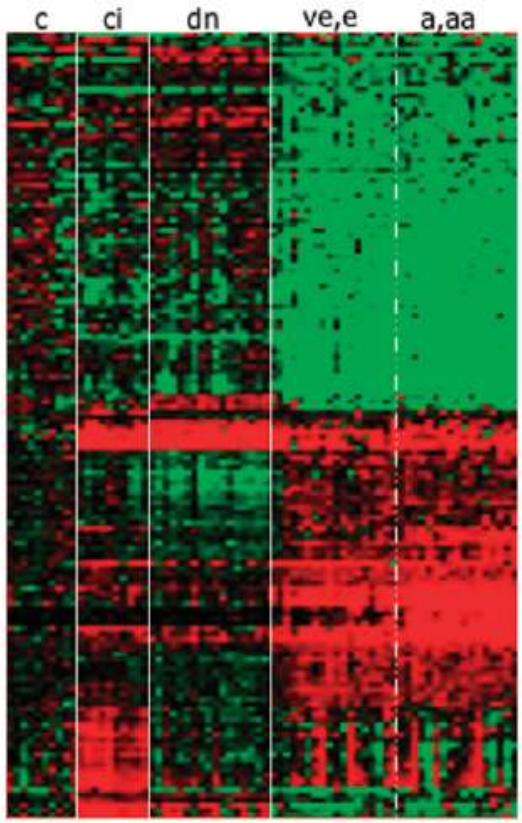


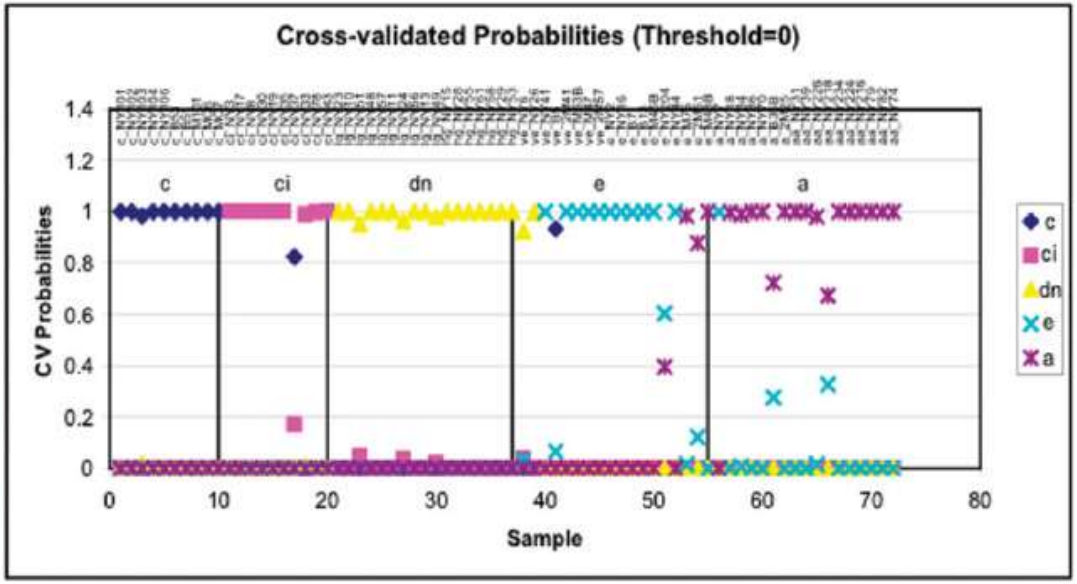


cDNA microarray (HBV infection)	Real-time RT-PCR (HCC)	Proteomics (metastatic HCC)
■ Oncogenes (↑) ▪ *c-MYC* ▪ *c-MYB* ■ Tumor suppressor genes (↓) ▪ *p53* ▪ *PTEN* ▪ *APC* ▪ *WAF1* ▪ *WT1*	■ Tyrosine kinases ▪ PDGFR-α ▪ Tie-2 ■ Growth factors ▪ IGF-2 ■ DNA modulators ▪ Topoisomerase IIα ▪ Telomerase RT	■ Cytokeratin

1. Wang XW et al. Toxicology. 181-182:2002;181/182:43-47. 2. Lee J-S et al. Hepatology. 2004;40:667-676. 3. Paradis V et al. Am J Pathol. 2003;163:733-741. 4. Ding S-J et al. Mol Cell Proteomics. 2004;3:73-81.

Genome-Wide Molecular Profiles of HCV-Induced Dysplasia and HCC





Group	SAM	PAM (Threshold)	No. of Genes in the Signature
Control (n = 10) vs. cirrhosis (n = 13)	112	9 (7)	8
Cirrhosis vs. dysplasia (n = 17)	29	59 (4.6)	24
Dysplasia vs. early HCC (n = 18)	104	350 (3.8)	93
Early HCC vs. advanced HCC (n = 17)	9	120 (3.5)	9
Dysplasia vs. HCC (n = 35)	693	61 (5.9)	53

Wurmbach E et al Hepatology 2007;45:938-947

Conclusion pre-LT HCC therapies

- No evidence for benefit of pre-LT treatment
- Evidence for complete necrosis in some patients
- Required randomized studies
- No data on seeding from transarterial techniques
- Seeding does occur after percutaneous techniques

Therapies for HCC

- Limited access to transplantation (Milan criteria)

- Resection – good patient, good surgeon, strict criteria

- Locoregional – unresectable disease – better than no therapy
  - RFA best lesions ≤4cm
  - TACE standardise method – DEB beads
  - TAE has smallest beads 45-100 μm, maybe as good
  - pre-transplantation – little data
  - combined therapies – need trials

Therapies for HCC

- **Radionuclides – when main portal vein thrombosis**

  - as first line therapy need more data

- **Sorafenib – in combination with loco-regional therapies**

  – when locoregional therapies not possible