Invasive procedures in the diagnosis and treatment of liver diseases: focal lesions

F.Farinati

Gastroenterologia, Padova

TACE: coming of age?

AISF 2005

TACE: LEVELS OF EVIDENCE

EBM

Degree of certainty	Methodology
A 1a	Metanalysis of homogenous RCTs
A 1b	Single RCT with accettable CI
A 1c	Metanalysis of homogenous cohort studies
B 2b	Cohort study or low quality RCT (f.u. <80% pts)
B 3a	Metanalysis with heterogeneity
B 3b	Case-control study
C 4	Observational or low quality case-control
D 5	Experts' opinion

TACE: coming of age?

- TACE IN INTERMEDIATE STAGE HCC
- TACE IN THE NEO-ADJUVANT TREATMENT FOR OLTx
- TACE COMBINED WITH LOCOREGIONAL TRANS-PARIETAL TREAMENTS (PEI-RFA)

TACE: coming of age?

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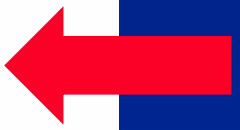
Barcelona staging system(BCLC)

Table 2. Barcelona Clinic Liver Cancer Classification

Stage	Performance Status Test	Tumor Stage	Okuda Stage	Liver Function Status
A	0	Single	I-II	Child-Pugh A-B
B	0	Large multinodular	I-II	Child-Pugh A-B
C	1-2	Vascular invasion/extrahepatic spread	I-II	Child-Pugh A-B
D	3-4	Any	III	Child-Pugh C

NOTE. Stage A and B, all criteria should be fulfilled; stage C and D, at least one criteria.

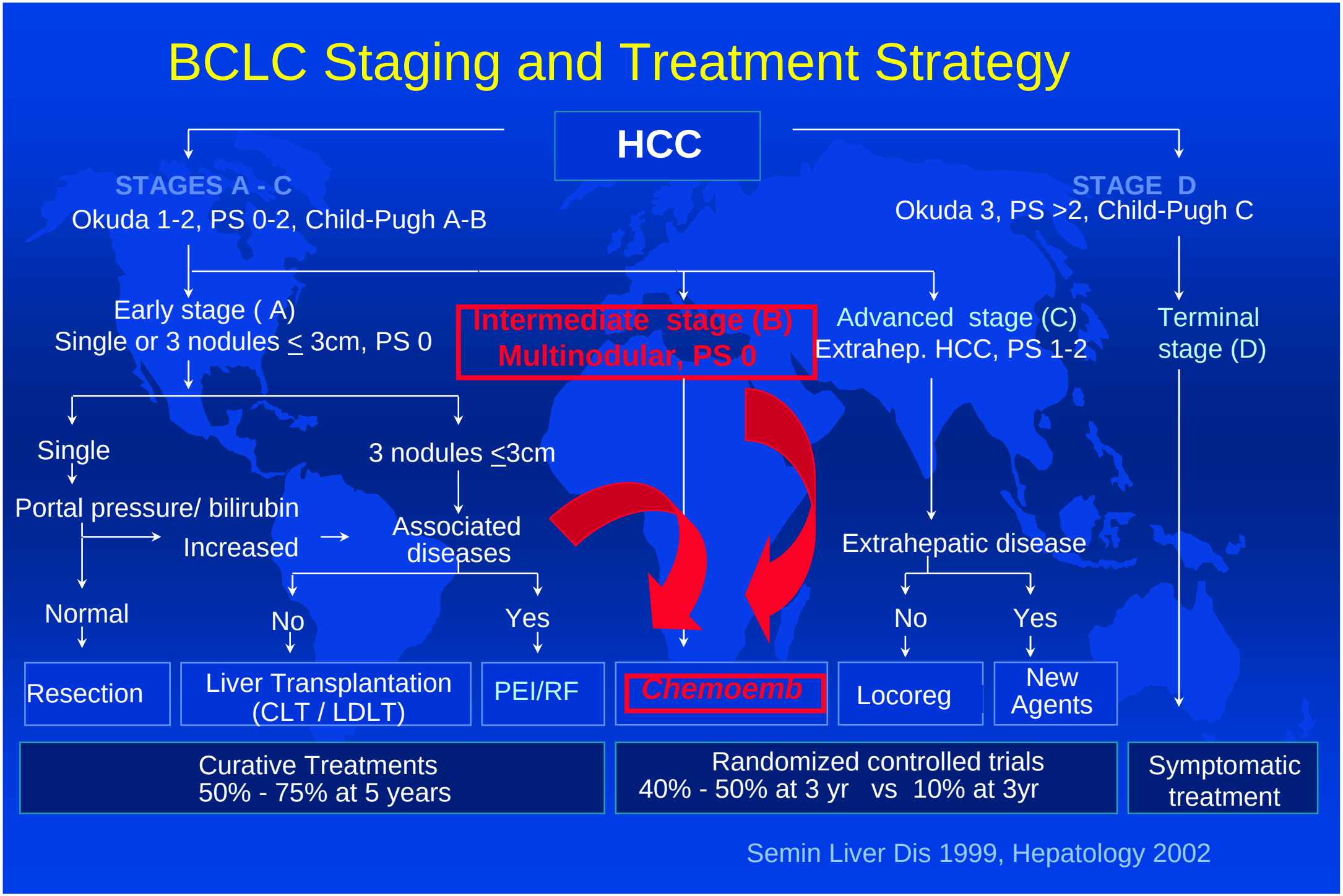


CLIP scoring system

	Score		
Variable	0	1	2
Child-Pugh	A	B	C
Tumor morphology	Uninodular < 50%	Multinodular < 50%	Massive or > 50%
AFP (ng/dL)	< 400 ng/dL	> 400 ng/dL	
Portal thrombosis	No	Yes	

Score 0-2

BCLC Staging and Treatment Strategy



Semin Liver Dis 1999, Hepatology 2002

How long is untreated natural history in the intermediate stage?

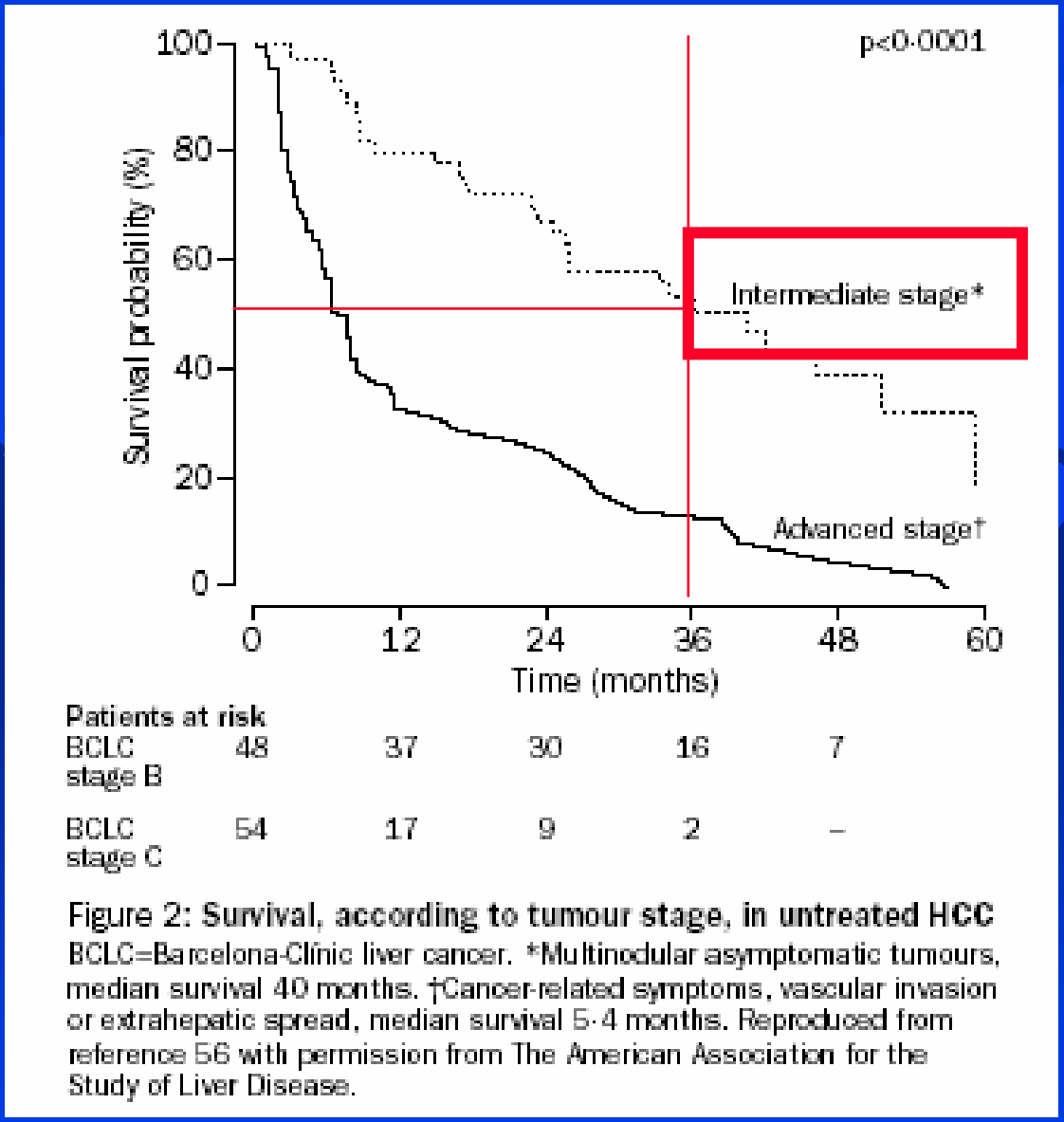


Figure 2: Survival, according to tumour stage, in untreated HCC
BCLC=Barcelona-Clínic liver cancer. *Multinodular asymptomatic tumours, median survival 40 months. †Cancer-related symptoms, vascular invasion or extrahepatic spread, median survival 5·4 months. Reproduced from reference 56 with permission from The American Association for the Study of Liver Disease.

Survival in untreated HCC patients

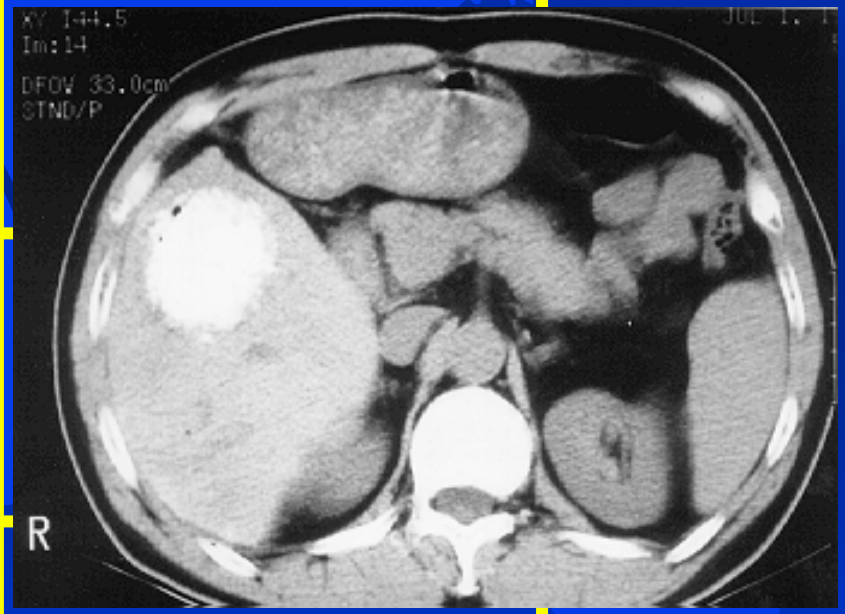
Llovet, Lancet 2003

Intermediate stage HCC ?

	I year survival	II year survival	III year survival
BCLC I°	80%	65%	50%
BCLC II°	63%	27%	17%
ITALICA J.I.M.	47%	28%	14%

HCC “advanced”: TACE

EASL	AISF
Additional trials needed	Segmentary or sub-segmentary
Bruix, EASL 2001	Not adeguate RCTs



TACE: indications and contraindications

PRO:

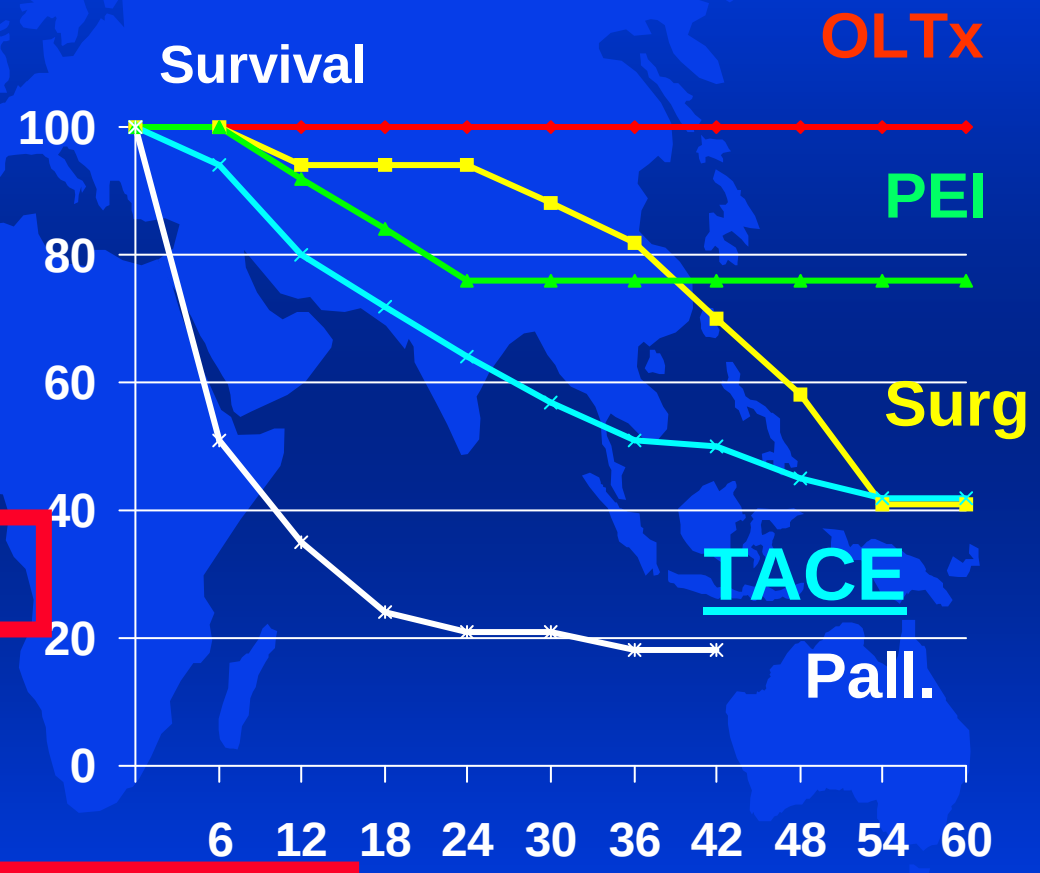
- Single node / no surgery or PEI-RFA;
- Multiple nodes;
- Child A and B (?);
- Patent portal tract;
- No high grade varices.

CONTRA:

- Portal thrombosis/artero-portal fistula/blood flow inversion;
- vascular abnormalities;
- Child C;
- Severe discoagulopathy
- Renal failure
- Extra-hepatic metastases.

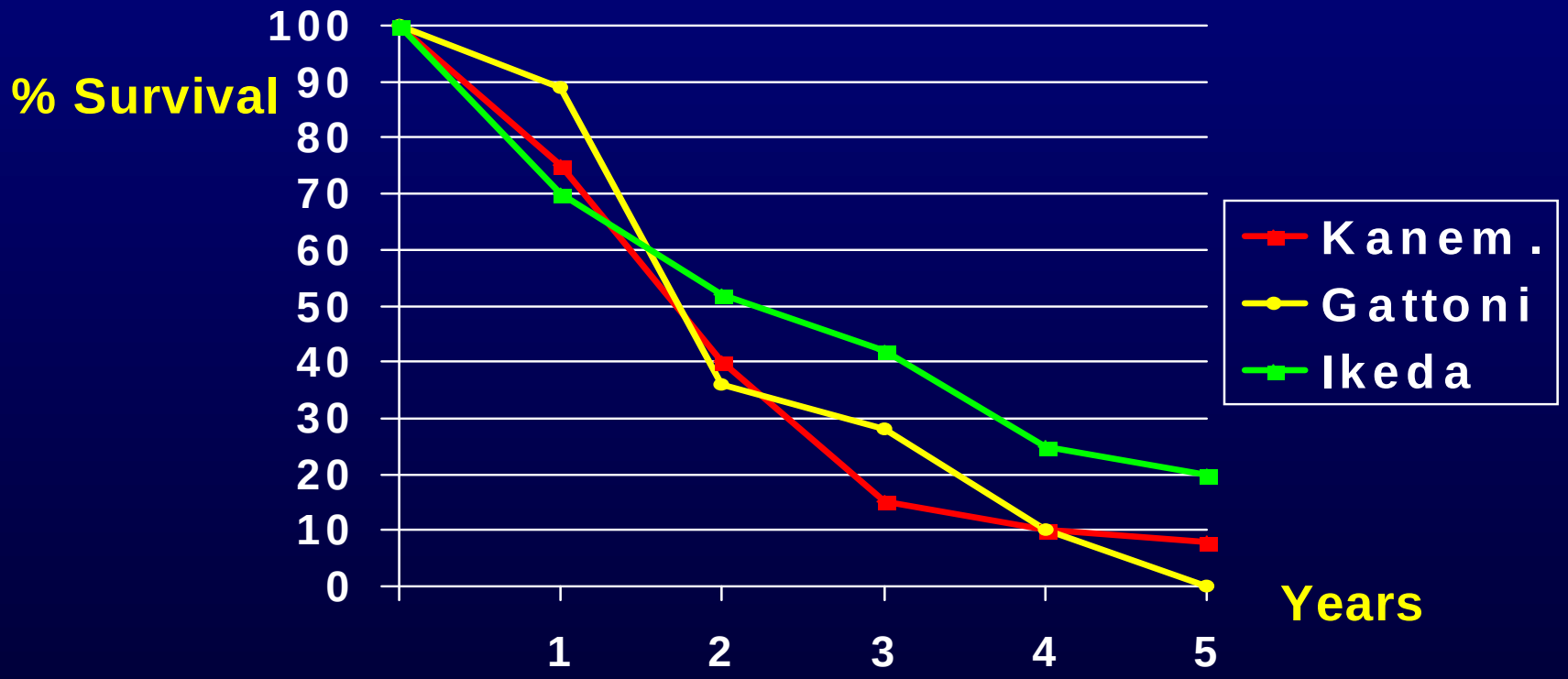
TACE: size of the problem

TREATMENT	SCREEN	CHANCE
OTLx =	4 (5%)	0 (0%)
Surg =	14 (17%)	5 (6%)
PEI =	9 (11%)	4 (5%)
TACE =	48 (59%)	42 (51%)
Pall. =	6 (7%)	31 (38%)



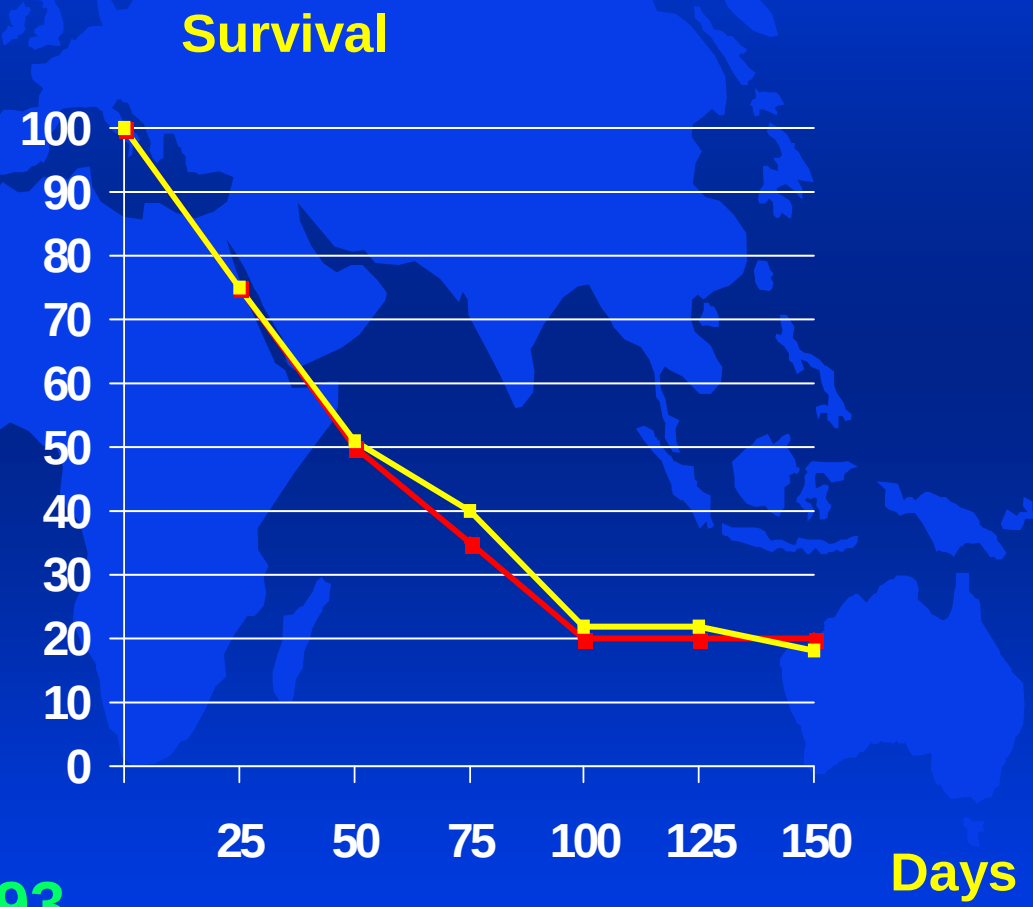
12% according to BRUIX, 2004

TACE: survival in open design studies



TACE: randomized studies

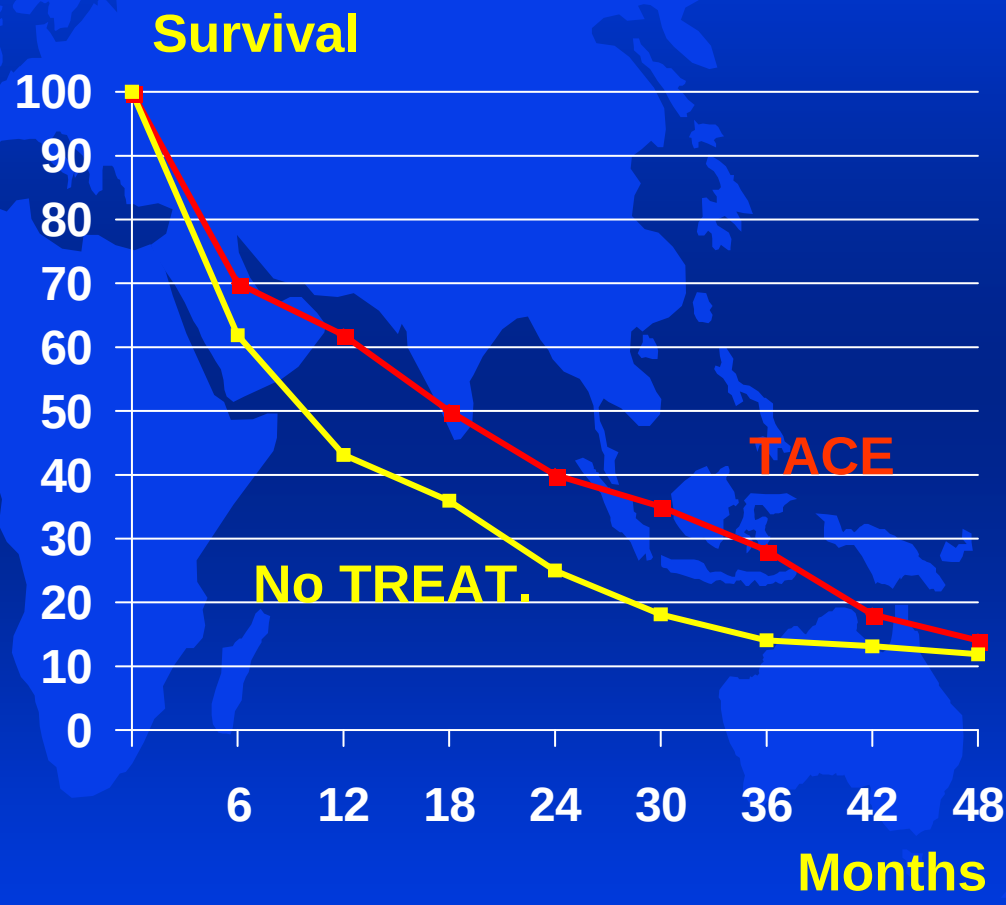
- No difference in survival between treated and untreated patients (short survival, no embolization, 75% Okuda II patients)



Madden, GUT 1993

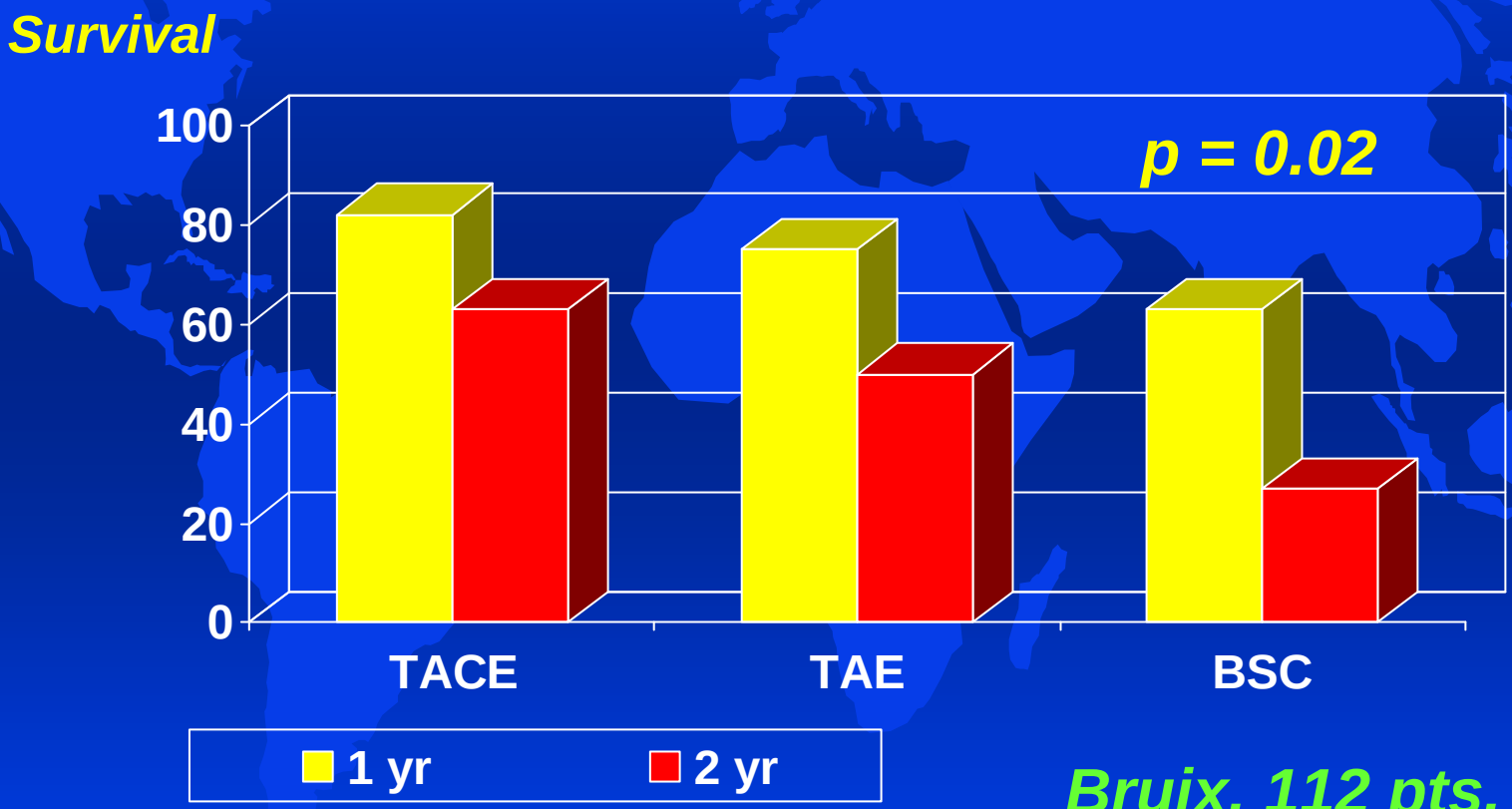
TACE: randomized studies

- 96 pts in 24 centers (4 pts/unit)
- 15 deaths in the first 2 months (Child A)
- 1 course/2months
- p = 0.1
- 53% of treated patients had tumor reduction, only 7% (versus 74%) had portal thrombosis.



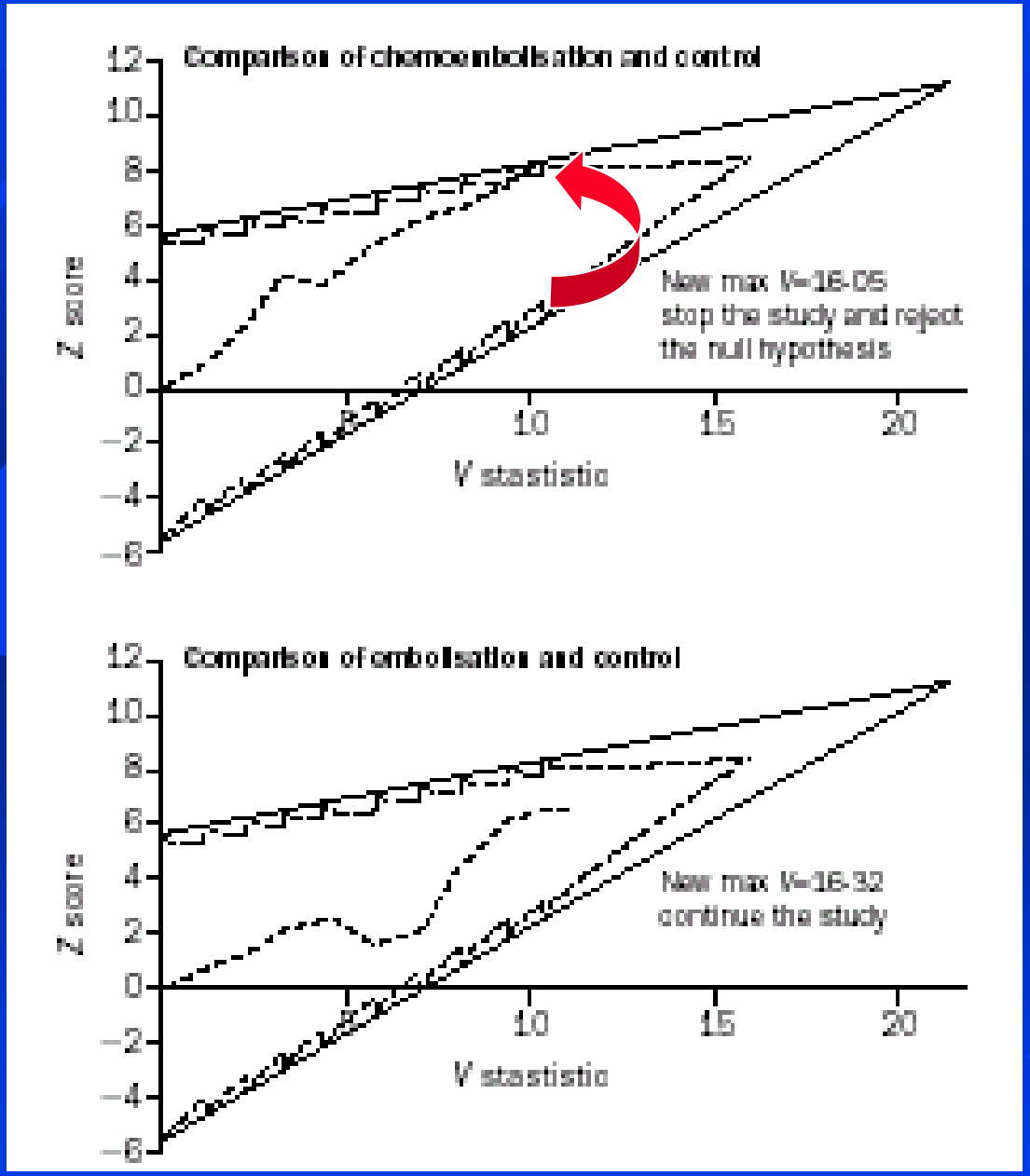
Group Etude Trait. Carcinome Hepatocell., NEJM 1995

TACE: randomized studies



Bruix, 112 pts, Lancet, 2002

Sequential design randomized trial



Radiology

Evidence-based Practice

Calogero Cammà, MD
Filippo Schepis, MD
Ambroglo Orlando, MD
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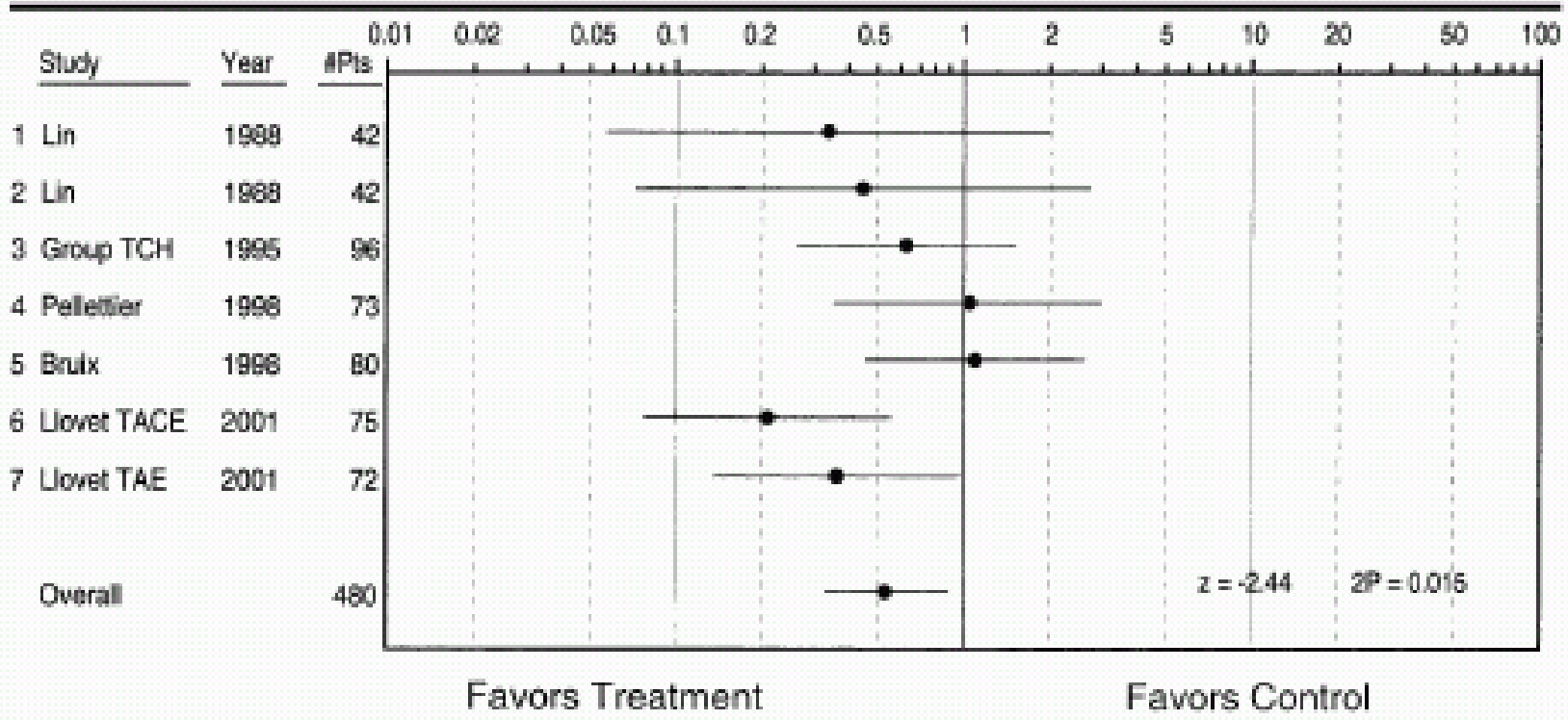
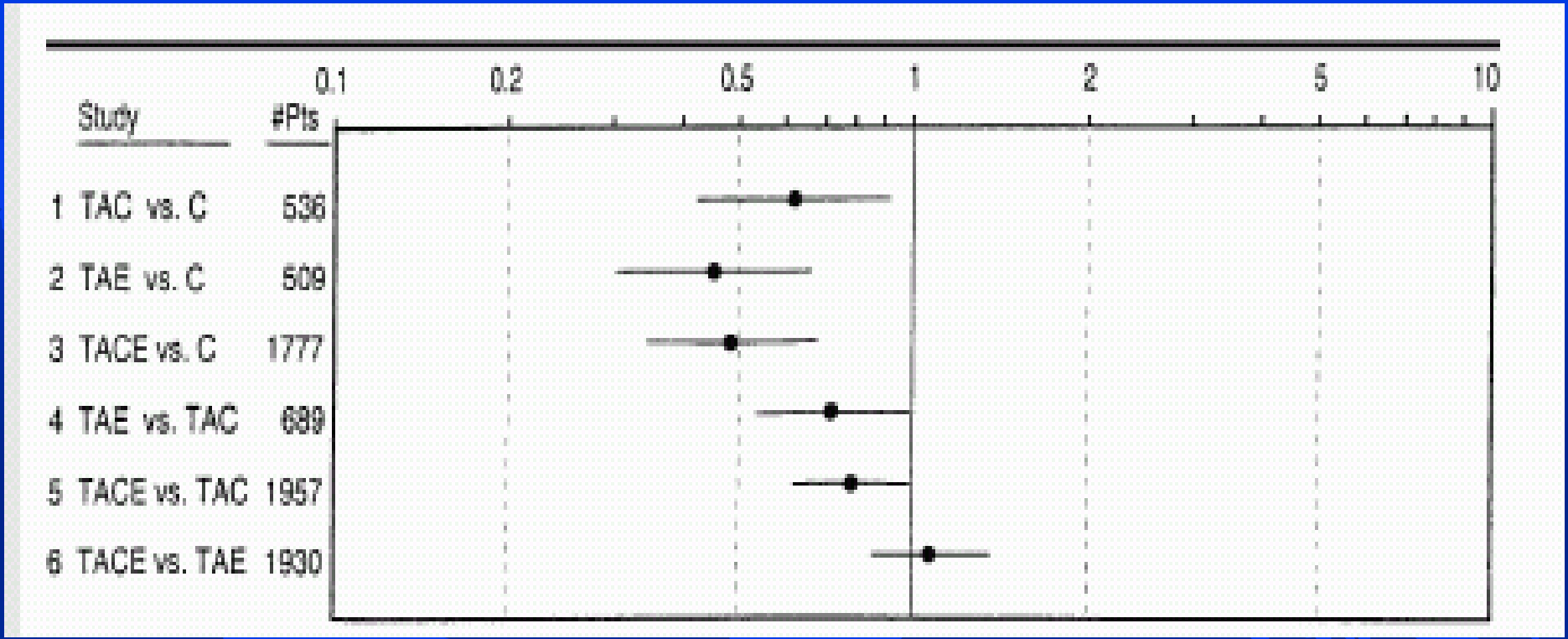
Lillian Shahied, PhD
Franco Trevisani, MD
Pietro Andreone, MD
Antonio Craxi, MD
Mario Cottone, MD

Index terms:
Efficacy study
Liver neoplasms, 761.323
Liver neoplasms, chemotherapeutic

Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: Meta-Analysis of Randomized Controlled Trials[1]

Radiology





The available evidence is sufficient to conclude that *(a)* chemoembolization significantly reduces overall 2-year mortality in patients with unresectable HCC and *(b)* TACE was not more effective than TAE, which suggests that the addition of the chemotherapeutic agents currently used does not improve the benefit of therapy and emphasizes the need for more effective anticancer drugs. Future

Mean CR rate 6%

Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival

Josep M. Llovet and Jordi Bruix for the Barcelona-Clinic Liver Cancer Group

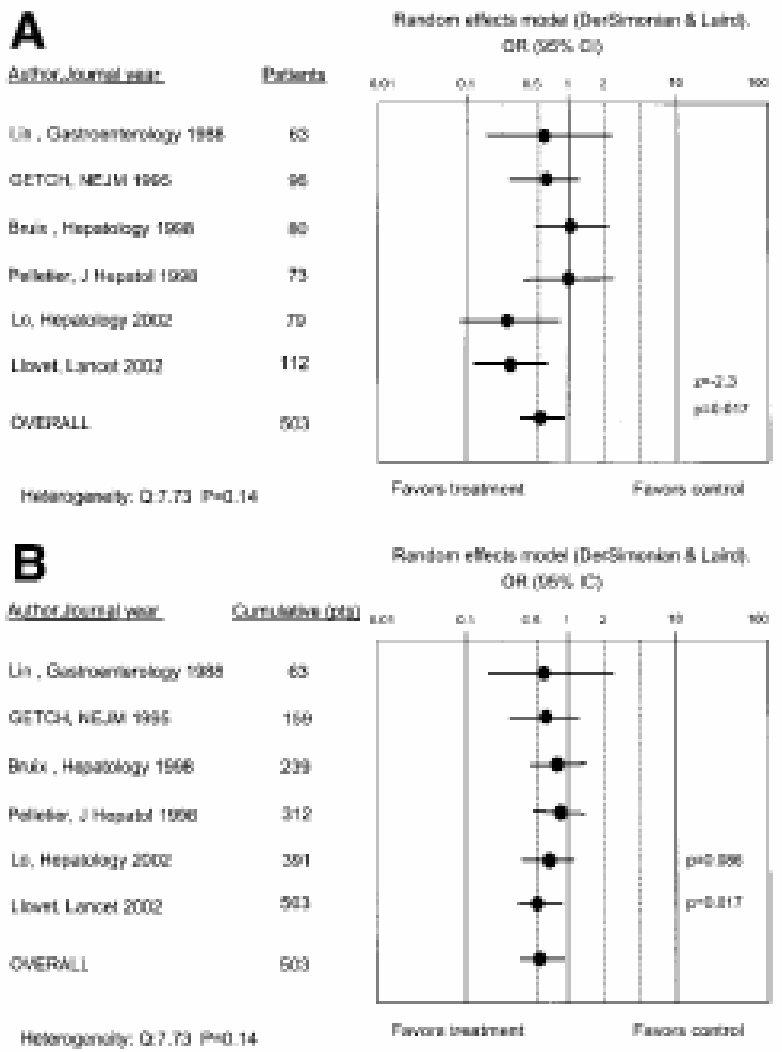


Fig. 2. (A) Meta-analysis of RCTs comparing 2-year survival with chemoembolization/embolization versus conservative management or suboptimal therapies for unresectable HCC (core group). Random effects model (OR, 0.53; 95% CI, 0.32-0.89; $P = .017$). (B) Cumulative meta-analysis according to time of publication.

Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival

Josep M. Llovet and Jordi Bruix for the Barcelona-Clinic Liver Cancer Group

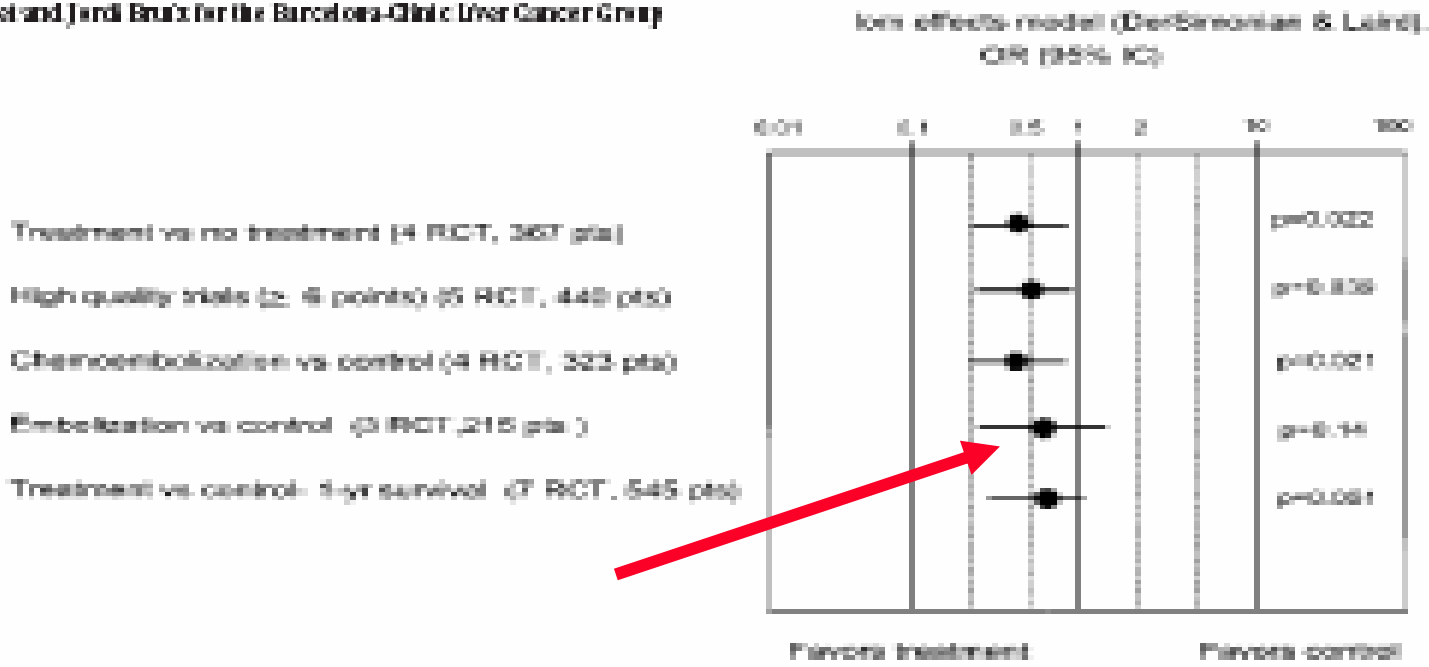


Fig. 3. Sensitivity meta-analysis of the core group (6 RCTs) reporting 2-year survival assessing embolization of RCTs with a control arm of conservative management (4 RCTs),[20,29,32,33] the effect of chemoembolization (4 RCTs),[20,31-33] embolization (3 RCTs),[27,30,32] and high-quality trials (5 RCTs).[29-33] Sensitivity analysis including all studies reporting 1-year survival rates (7 RCTs).[27-33]

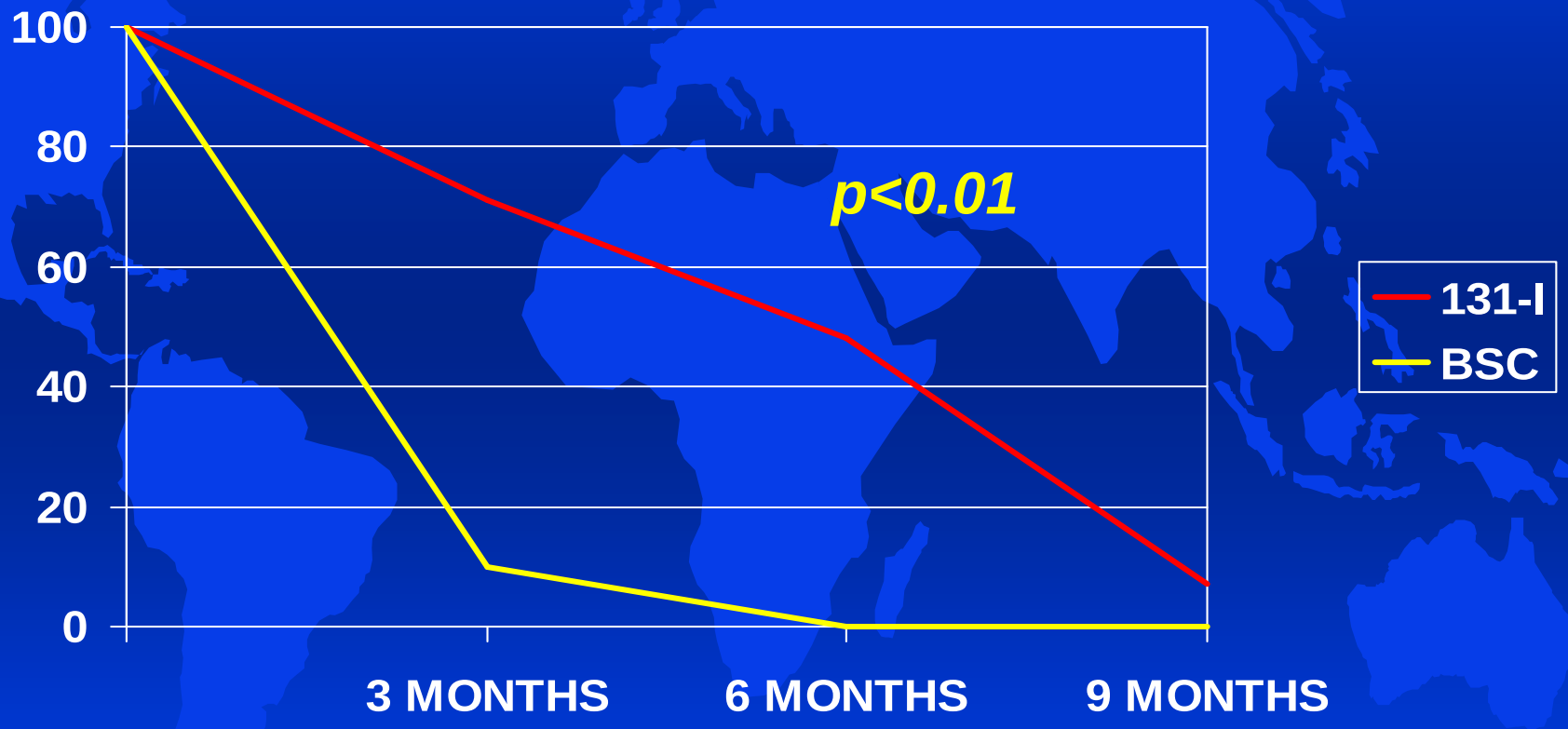
Table 4. Predictors of Survival in Patients With HCC Treated by Arterial Embolization/Chemoembolization, Multivariate Analysis

Author, journal (n)	Variables	*P*
Arterial emboliation/chemoembolization		
Mondazzi et al., Hepatology 1994[51] (n = 84)		
	Age	<.01
	Child-Pugh	<.05
	Serum bilirubin	<.025
	Tumor size	<.001
	Degree of lipiodol labelling	<.01
GETCH, N Eng J Med 1996[14] (n = 96)		
	Karnofsky score	.004
	Ascites	<.001
	Serum albumin	.004
	Tumor type	.02
	Tumor mass	<.001
	Segmental portal obstruction	<.001
	Serum AFP	.009
Bruix et al., Hepatology 1998[15] (n = 80)		
	Performance Status test	.005
	Serum bilirubin	.05
Llovet et al., Lancet 2002[18] (n = 112)		
	Baseline variables (n = 112)	
	Treatment allocation	.02
	Inclusion of treatment response (n = 102)	
	Treatment response	.0007
	Constitutional syndrome	.04
Lo et al., Hepatology 2002[17] (n = 79)		
	Treatment allocation	.006
	Portal vein thrombosis	.004
Arterial embolization and percutaneous ablation		
Tanaka et al., Cancer 1998[52] (n = 83)		
	Child-Pugh	<.001
	Tumor diameter	.003

TACE: relevant problems

- **Schedule**: 1/ 6 weeks to 2-3 months, “a la demande” ?
- **Sections**: bilat. involvement, 1 course/lobe
- **Monitoring**: liver function, pancreatic damage, glucose homeostasis, thyroid function,US appearance (contrast media?).
- **Treatment**: antibiotics, insulin, drainage.
- **Stop**: progression, avascular lesions, complete response, liver failure
- **Morbility (major):** 10% (ischemic colecystitis, pancreatitis, liver abscess)
- **Mortality**: 1-5%
- **?????** Chemotherapeutic agent, embolizing tool.

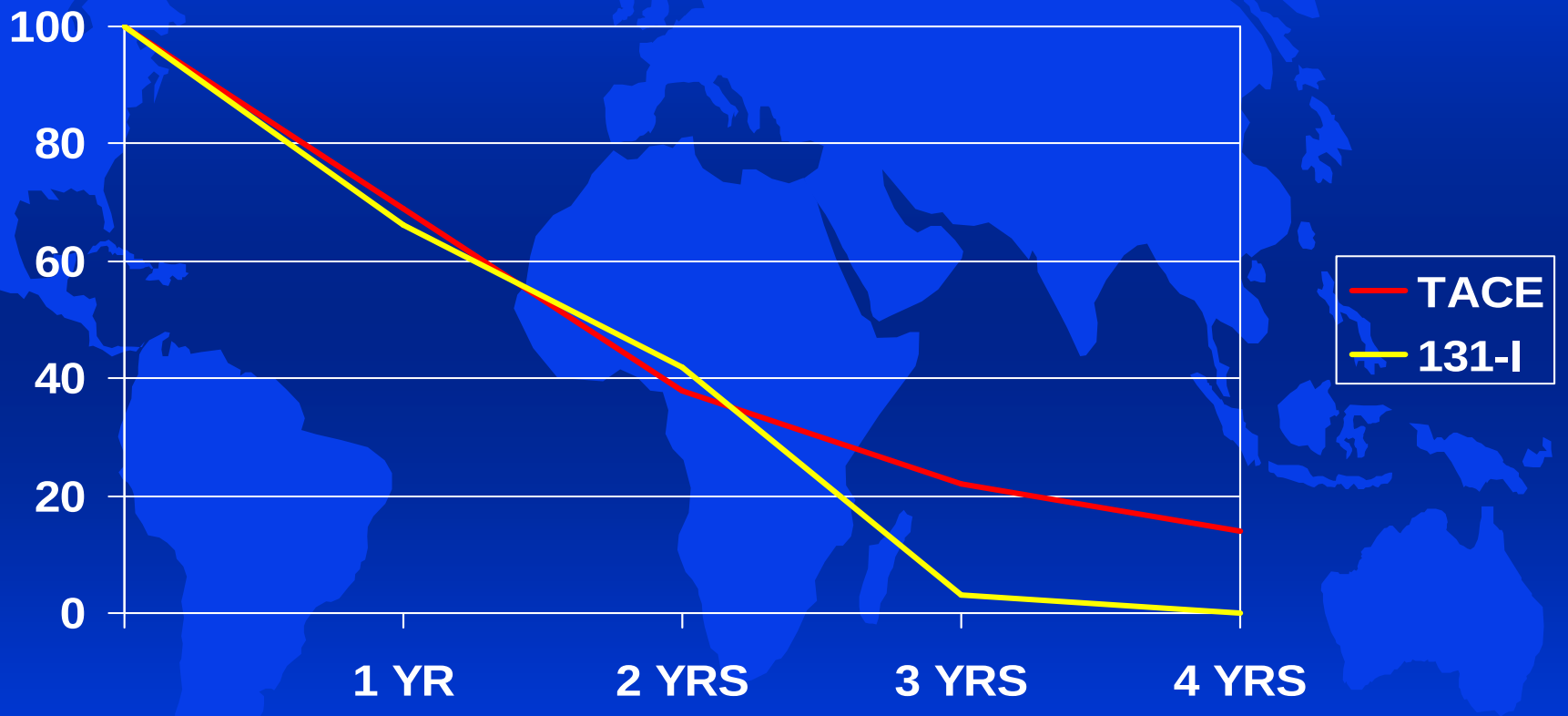
Radioactive-lipiodol Embolization (RCTs)



Raoul, J.Nucl.Med., 1994

GOOD TOLERANCE!

RADIO-ACTIVE LIPIODOL INJECTION (RCTs)



Raoul, Hepatology, 1997

BETTER TOLERANCE!

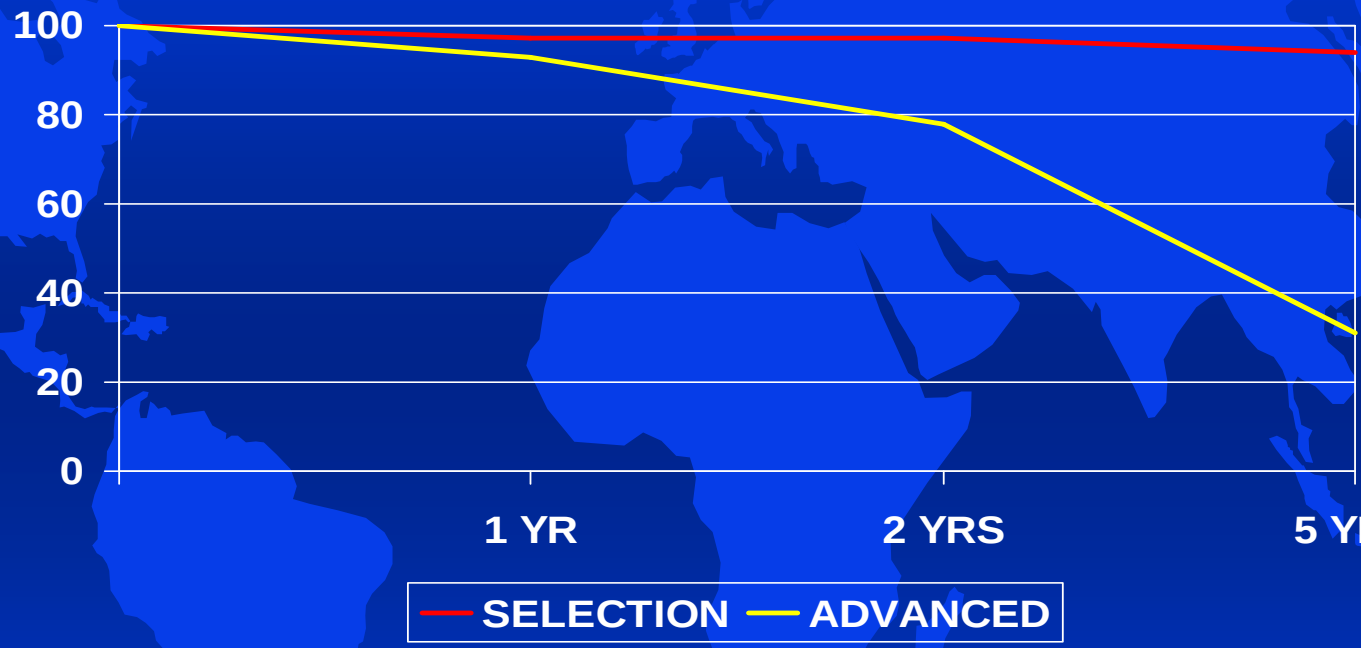
TACE: coming of age?

- TACE IN INTERMEDIATE STAGE HCC
- TACE IN THE NEO-ADJUVANT TREATMENT FOR OLTx
- TACE + LOCOREGIONAL TRANS-PARIETAL TREAMENTS (PEI-RFA)

TACE ad OLTx

- Multivariate analysis of predictor of survival in 67 HCC patients shows that neo-adiuvant chemoembolization reduces the risk of death (Shimoda, 2004)
- Aggressive ablation treatment…. optimizes the use of OLTx in HCC patients (Fisher 2004)

TACE ad OLTx



Advanced with TACE

TACE is highly efficacious in preventing tumor progression and is associated with excellent outcome. No beneficial effect despite downstaging in advanced HCC

Graziadei, 2003

OLT x for HCC: The AISF experience

HCC transplanted: 1985-1999

587/3026 pts *(20%)*

Males: 505

Females: 82

HCC = 6.2

M/F

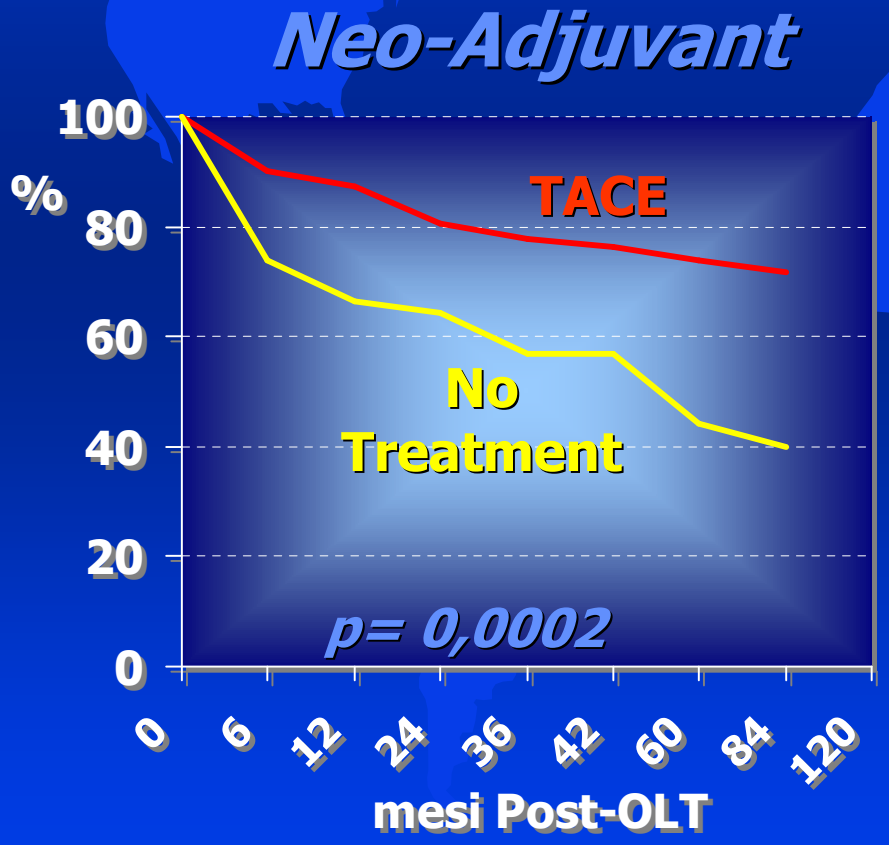
General=2.3

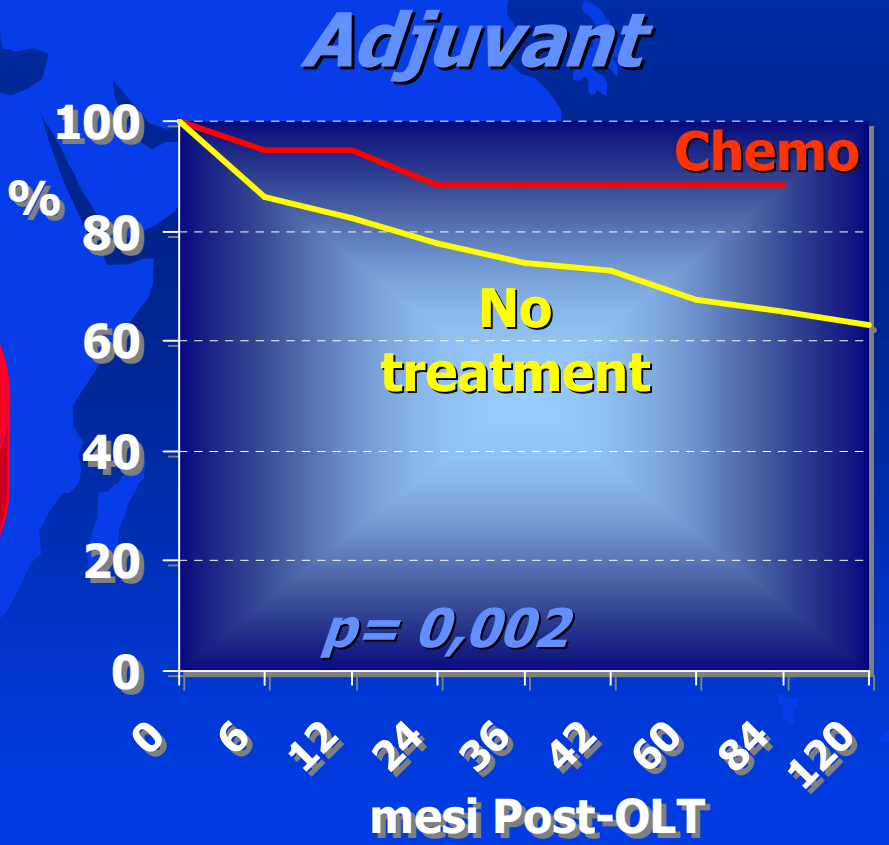
Mean age: 51,8 *(range: 19-72)*

"Monotematica AISF Liver Transplant Group"

OLTx and HCC: Survival

(Kaplan-Meier survival analysis)





Partial Necrosis on Hepatocellular Carcinoma Nodules Facilitates Tumor Recurrence after Liver Transplantation

Matteo Ravaioli,[1] Gian Luca Grazi,[1] Giorgio Ercolani,[1] Michelangelo Fiorentino,[2] Matteo Cescon,[1] Rita Golfieri,[3] Franco Trevisani,[4] Walter Franco Grigioni,[2] Luigi Bolondi,[5] and Antonio Daniele Pinna[1,6]

Transplantation 2004

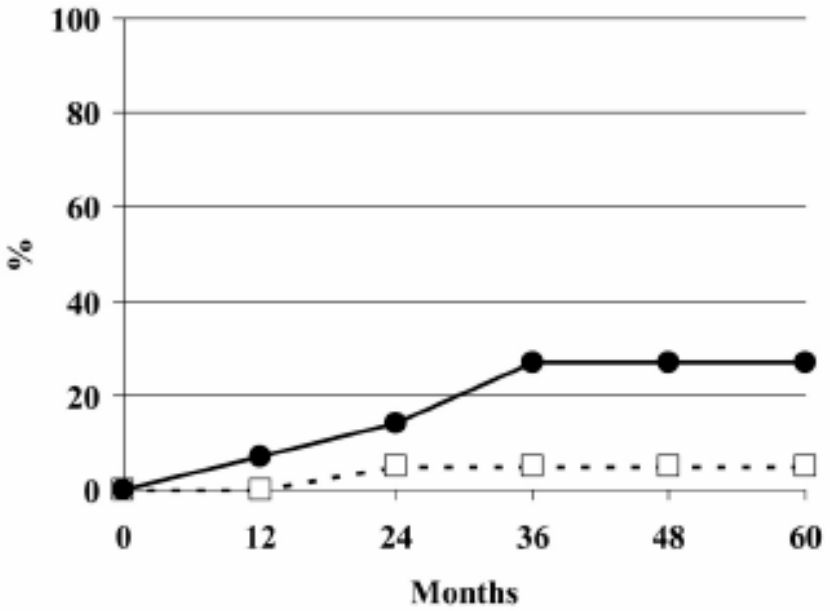


FIGURE 1. Cumulative incidence of recurrence according to the presence of partial necrosis (partial necrosis ●; no partial necrosis □).

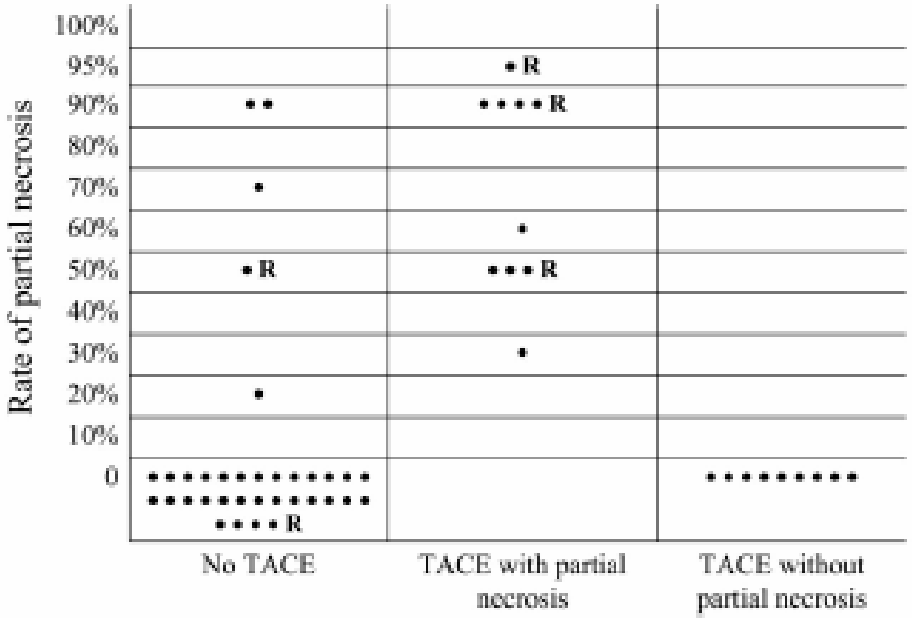


FIGURE 2. Rate of partial necrosis and Hepatocellular Carcinoma recurrences (R) distributed according to the transarterial chemoembolization (TACE) procedure (No. cases ●).

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• BRIEF REPORTS •

Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level

Xin Li, Gan-Sheng Feng, Chuan-Sheng Zheng, C

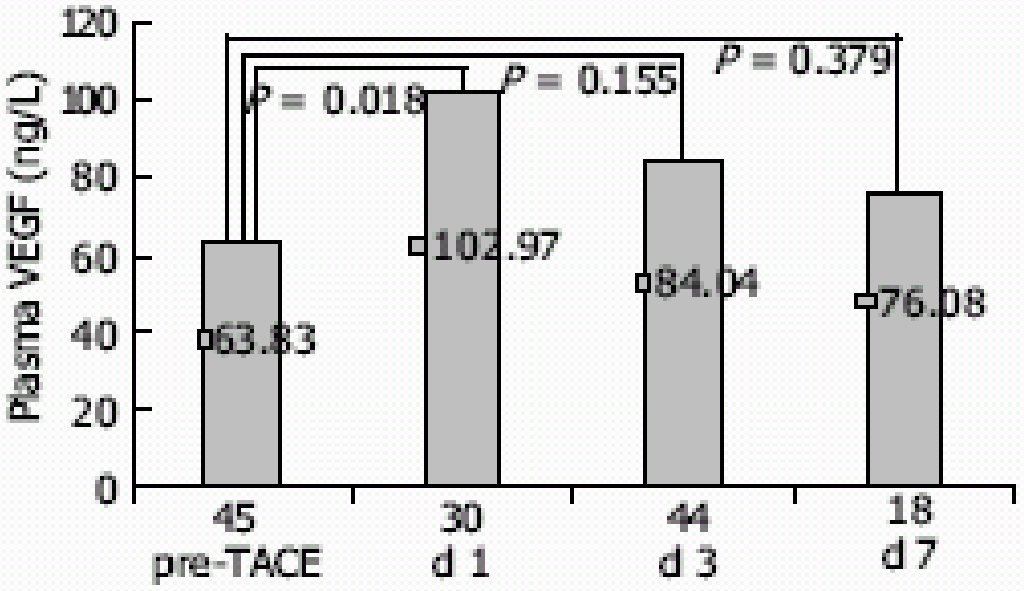


Figure 2 Effect of TACE on mean plasma vascular endothelial growth factor levels.

TACE: coming of age?

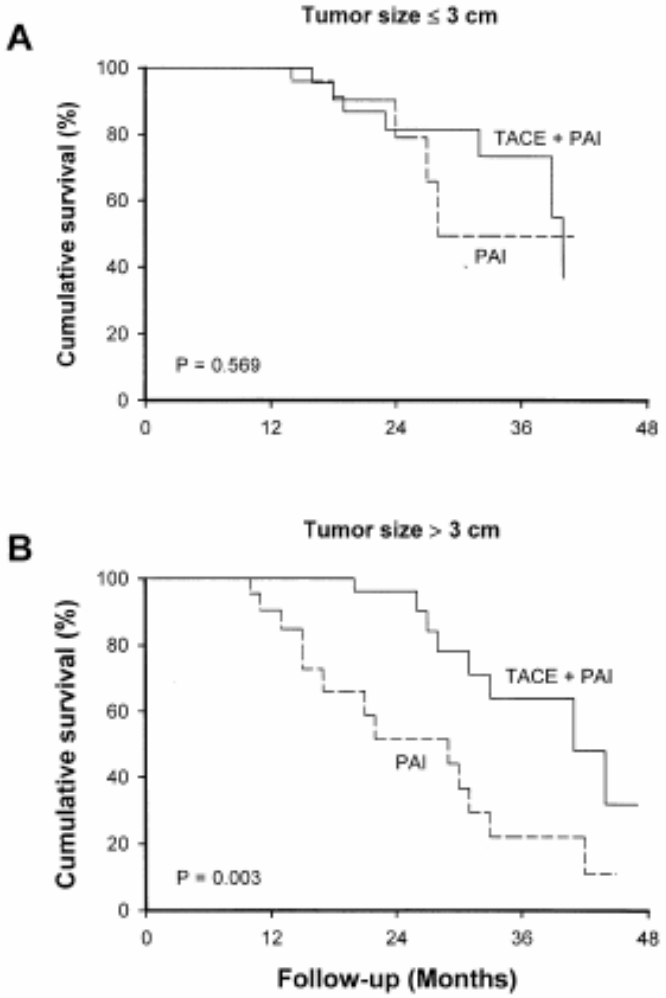
- TACE IN INTERMEDIATE STAGE HCC
- TACE IN THE NEO-ADJUVANT TREATMENT FOR OLTx
- TACE + LOCOREGIONAL TRANS-PARIETAL TREAMENTS (PEI-RFA)

Original article

Annals of Oncology 14: 1648–1653, 2003
DOI: 10.1093/annonc/mdg460

Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study

T.-I. Huo[1]* ... S.-D. Lee[1]



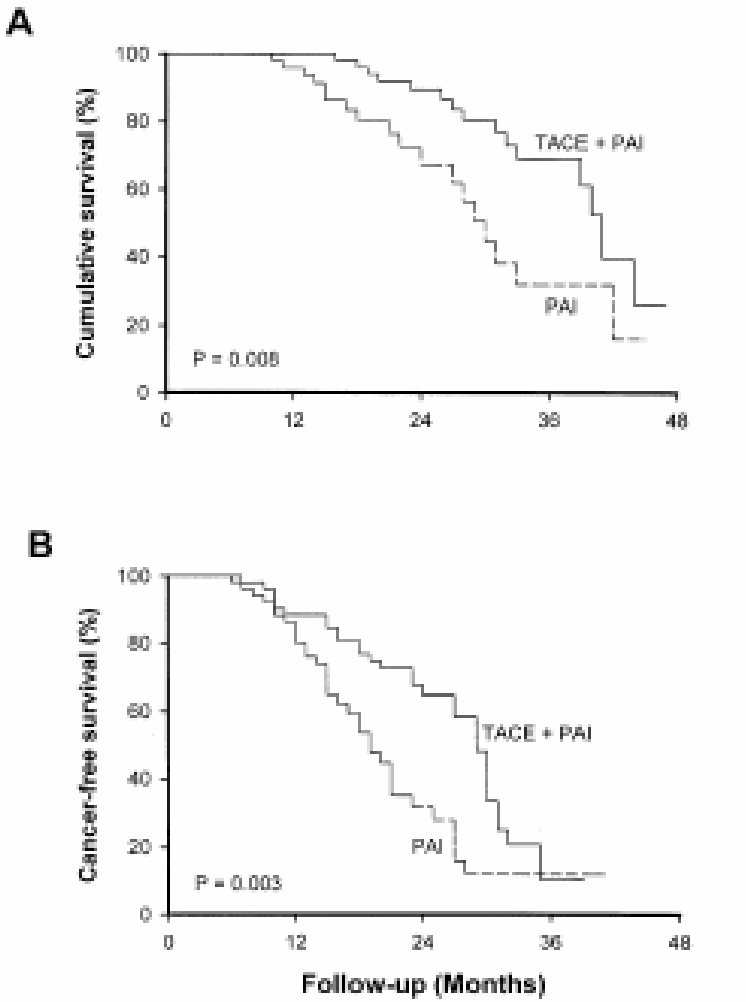


Figure 1. Comparison of (A) overall survival and (B) cancer-free survival between hepatocellular carcinoma patients treated with transarterial chemoembolization–percutaneous acetic acid injection (TACE–PAI) and PAI.

TACE-BASED COMBINATION TREATMENT IN LARGE HCC

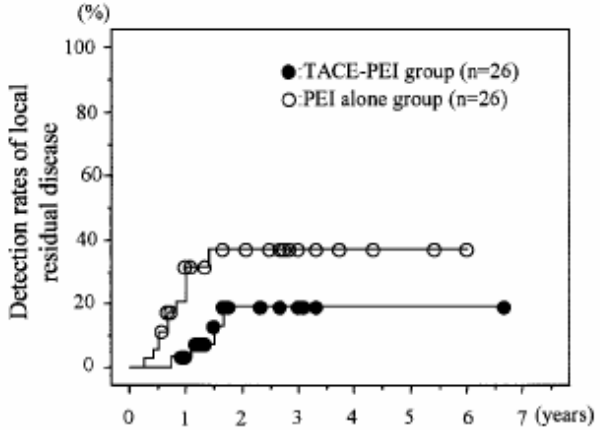
- Randomized controlled trial in 53 HCC pts comparing TACE + PEI versus repeated TACE. Combined treatment….
- Increases complete response
- Reduces tumor recurrence
- Correlates with longer survival (p=0.1)
- Correlates with longer D.F. survival

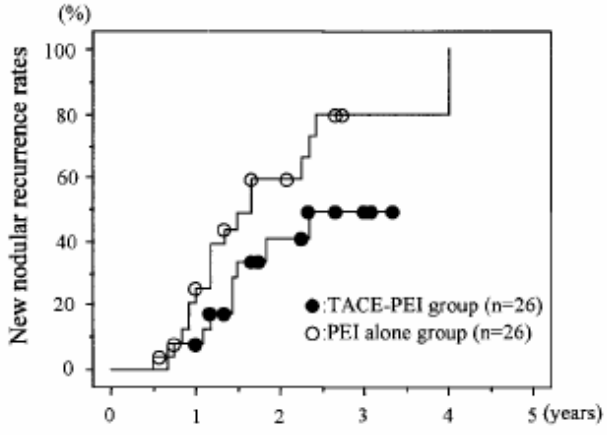
Bartolozzi, 1995

Combination Therapy with Transcatheter Arterial Chemoembolization and Percutaneous Ethanol Injection Compared with Percutaneous Ethanol Injection Alone for Patients with Small Hepatocellular Carcinoma

A *Randomized Control Study*

Masahiko Koda, M.D.
Toshikazu Murawaki, M.D.
Akeri Mitsuda, M.D.
Kenji Oyama, M.D.
Kinya Okamoto, M.D.
Yoko Idobe, M.D.
Takeaki Suou, M.D.
Hironaka Kawasaki, M.D.





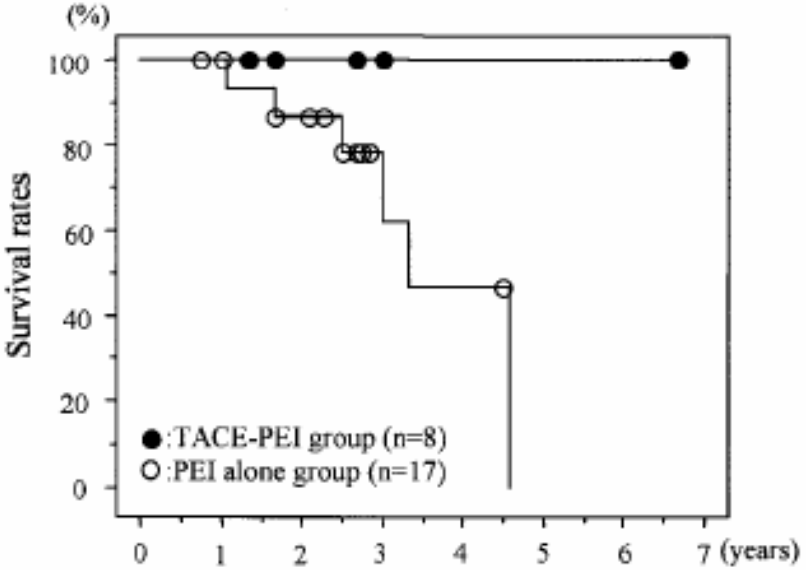


FIGURE 4. A comparison of the survival rates only in patients with hepatocellular carcinoma (HCC) tumors measuring < 2 cm in greatest dimension between the group that received transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI) (TACE-PEI group) and the group that received PEI alone (PEI alone group). The survival rate in the TACE-PEI group was higher than that in the PEI alone group ($P < 0.01$).

In summary….

Despite lack of standardization, TACE….

- ***Is effective in prolonging survival in selected HCC patients in the intermediate stage (A1a)***
- ***Is effective in reducing drop-out rate and increasing survival in HCC patients undergoing OLTx (B2b)***
- ***When associated with percutaneous treatments, is effective in increasing response rate and prolonging survival in (large) HCC (A1b-B2b)***

Thanks !