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Management of hepatocellular carcinoma in 2015

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Evolving Concepts in the Clinical Management of Hepatocellular Carcinoma

2001 EASL

Journal of Hepatology 35 (2001) 421–430
**Clinical Management of Hepatocellular Carcinoma.
Conclusions of the Barcelona-2000 EASL Conference**

2005 AASLD

AASLD PRACTICE GUIDELINE HEPATOLOGY, Vol. 42, No. 5, 2005
Management of Hepatocellular Carcinoma
Jordi Bruix¹ and Morris Sherman²

2010 APASL

GUIDELINES Hepatol Int (2010) 4:439–474
**Asian Pacific Association for the Study of the Liver consensus
recommendations on hepatocellular carcinoma**
Masao Omata · Laurentius A. Lesmana · Ryosuke Tateishi · Pei-Jer Chen · Shi-Ming Lin · Haruhiko Yoshida ·

2011 AASLD

AASLD PRACTICE GUIDELINE www.aasld.org
Management of Hepatocellular Carcinoma: An Update
Jordi Bruix¹ and Morris Sherman²

2012 EASL

Clinical Practice Guidelines European Journal of Cancer (2012)
**EASL–EORTC Clinical Practice Guidelines: Management
of hepatocellular carcinoma**
European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer

The Barcelona Clinic Liver Cancer (BCLC) Staging Classification for Hepatocellular Carcinoma

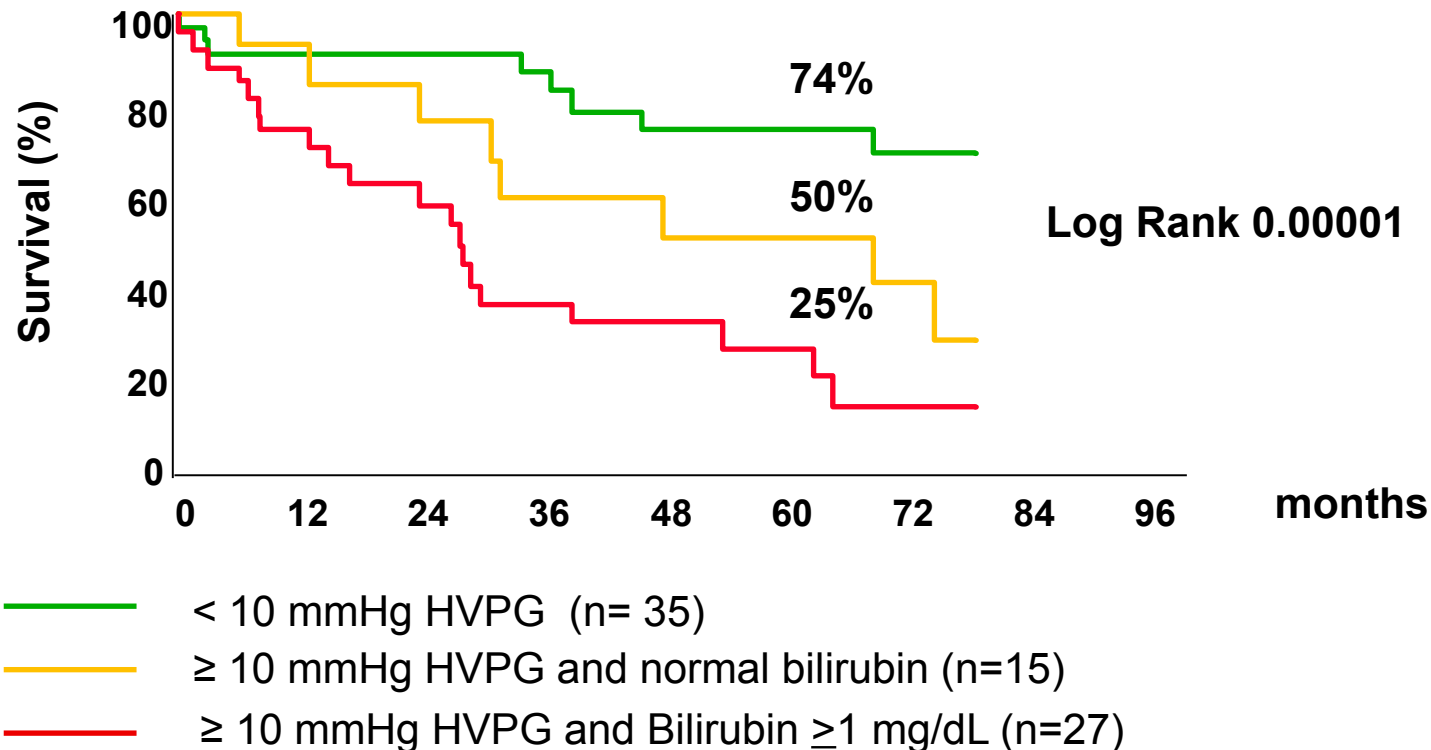
BCLC stage	Performance status	Tumor volume, number and invasiveness	Child-Pugh
0 Very early	0	≤ 2 cm vaguely nodular	A
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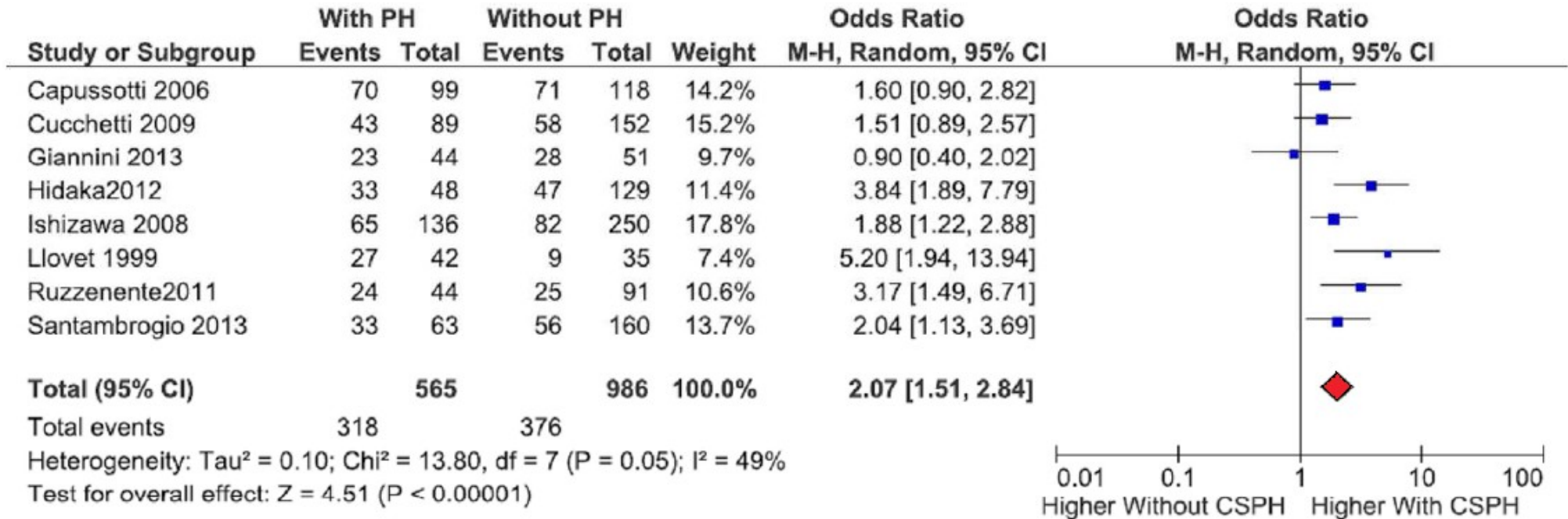
Early HCC: Survival after Resection Is Influenced by Portal Hypertension and Bilirubin

Best candidates for resection : Solitary HCC \leq 5 cm
Child-Pugh A: Low portal hypertension
Normal bilirubin



Portal Hypertension and Hepatic Resection for Small HCC

A Meta-analysis, 5-year Mortality

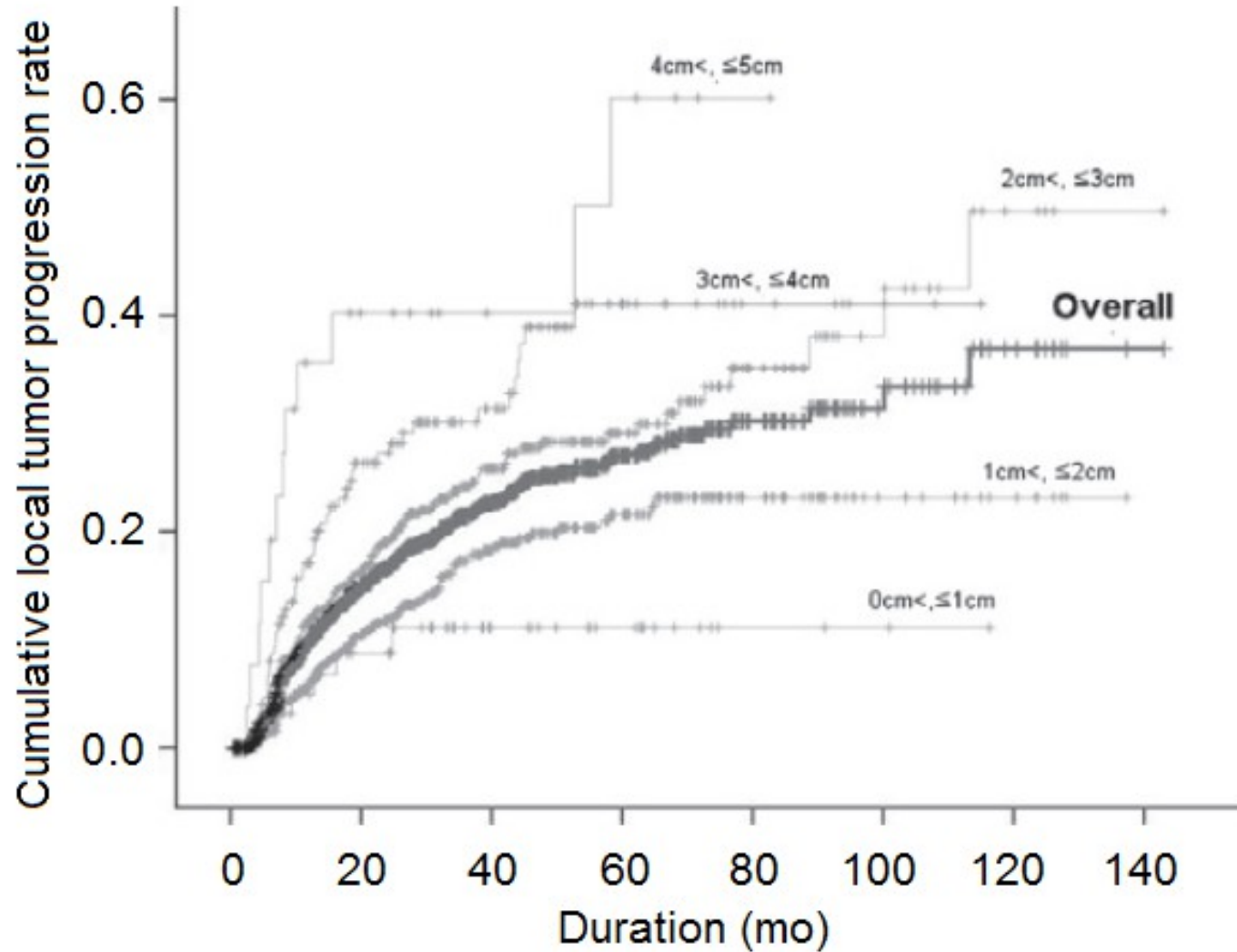


Radiofrequency Ablation in Child Pugh A Cirrhosis

The Importance of Tumor Number and Size

Tumor	N	Survival (%)				P-value
		1 yr	5 yr	10 yr	Median (yr)	
<u>Single</u>	685	97.2	64.6	32.0	7.0	P=0.0003
2-3	395	95.7	54.4	19.9	5.6	
≥ 4	90	96.5	53.6	17.6	5.3	
Single ≤ 3 cm	889	97.2	65.1	30.7	6.7	P<0.0001
> 3 cm	281	94.8	46.5	18.6	4.6	

Local Tumor Progression of 1462 HCCs after RFA as a First Line Therapy



Review Three-yr Survival Following Resection or RFA of HCC in Child Pugh A Cirrhosis

Tumor	No. of patients	HR	No. of patients	RFA	Results (95% CI)	Meta-analysis	
		Pooled estimate (%)		Pooled estimate (%)		p value	I ²
Single, ≤2 cm	1265/1361	89.4 (73.2-98.7)	1411/1477	89.4 (73.2-98.7)	1.03 (0.69-1.52)	0.949	91
Single, ≤3 cm	480/551	86.2 (77.7-91.7)	105/188	56.5 (47.9-64.9)	1.11 (1.03-1.19)	0.004	47
Single, >3 cm	37/55	66.4 (50.7-80.4)	86/122	65.1 (35.3-89.5)	1.22 (1.06-1.42)	0.007	0
Two-three, ≤3 cm	37/55	66.4 (50.7-80.4)	86/122	65.1 (35.3-89.5)	1.03 (0.69-1.52)	0.886	55

Radiofrequency is more cost-effective than resection in very early HCC and 2-3 nodules ≤ 3 cm

STORM RCT of Adjuvant Sorafenib after Curative Resection or Ablation

Outcomes	Sorafenib	Placebo	Hazard ratio (95% CI)	P-value
Recurrence free survival, mos	33.4	33.8	0.940 (0.780-1.134)	0.26
Time to progression, mos	38.6	35.8	0.891 (0.735-1.081)	0.12
<u>Overall survival, mos</u>	NR	NR	0.995 (0.761-1.300)	0.48
Tx-related Adverse events, %				
All grade	98	90		
Serious	40	42		

Selection Criteria In Liver Transplantation For HCC

Criteria

Definition

Milan (MC)

Single nodule ≤ 5 cm
Up to 3 nodules ≤ 3 cm
No macrovascular invasion

UCSF

Single ≤ 6.5 cm
Up to three nodules ≤ 4.5 cm
Sum of tumor diameter ≤ 8 cm

Up-to-7

Sum of size (cm) and number of HCC nodules ≤ 7
No mVI

TTV+AFP

Any nodule up to TTV ≤ 115 cm³
AFP ≤ 400 ng/mL

Milan + AFP

Score system based on number of nodules, size of the largest nodule, AFP at listing (<100; 100–1000; >1000 ng/mL)

Predicting Survival after Liver Transplantation in Patients with HCC beyond Milan Criteria

	No. of Patients (n=1556)	Milan in (n=444)	Milan out (n=1112)	P-value
No. tumors Median (range)	3 (1-20)	1 (1-3)	4 (1-20)	<0.0001
Max tumor size, mm Median (range)	35 (1-200)	20 (1-50)	40 (4-200)	<0.0001
Vascular invasion, n				
No	977 (66.2%)	361 (89.1%)	616 (57.6%)	<0.0001
Yes	498 (33.8%)	44 (10.9%)	454 (42.4%)	
Overall survival (95% CI) at 10 years	46.8% (43.0-50.5)	69.6% (63.7-74.8)	38.7% (34.2-43.1)	<0.0001

Salvage Liver Transplantation After Primary Hepatic Resection for HCC, Milan (\pm)

A review of 16 comparative/cohort studies

N=319	Patients
	Tumor size 2.5-3.4 cm
	Micro vs macrovascular: 28% vs 4%
18-29%	Major hepatectomy (0-6% deaths)
27-80%	Tumor recurrence
16-65%	Salvage Liver Transplantation (SLT)

SLT Complications	Biliary 8%
	Infection 11%
	Bleeding 8%
	Vascular 7%
	Deaths 6%
<u>Five-yr survival</u>	62% (41-89)

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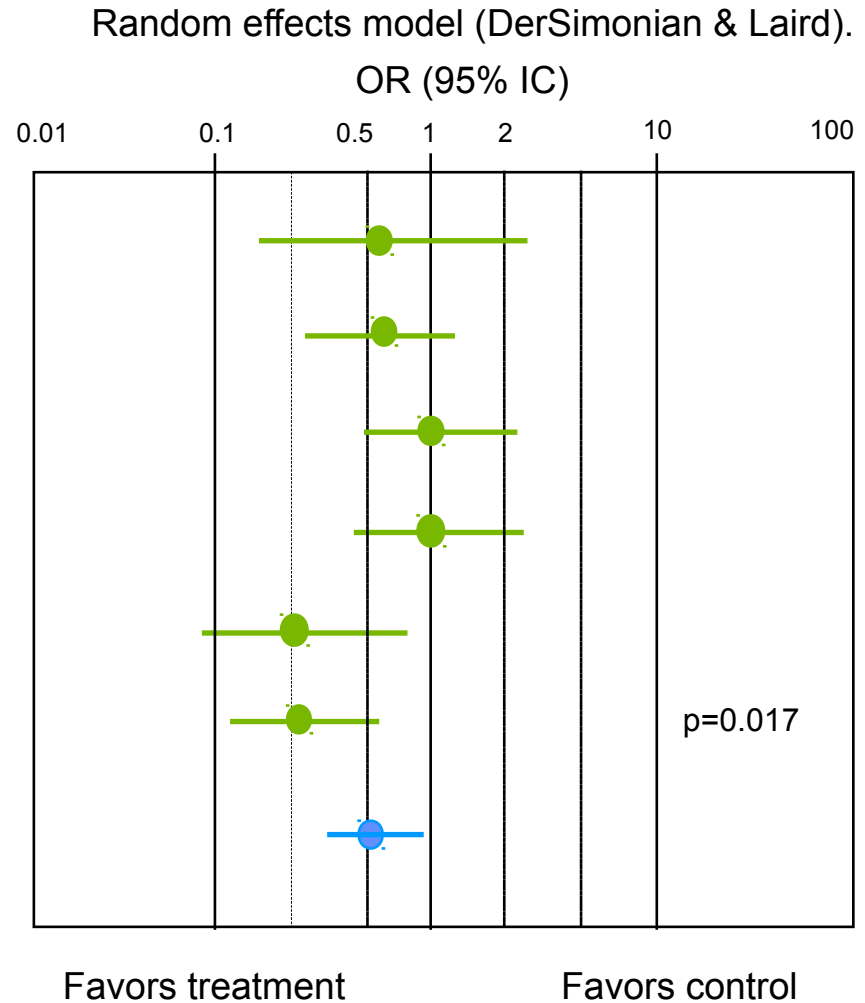
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Intermediate HCC: The Outcome of Chemoembolization

<u>Author,Journal year</u>	<u>Patients</u>
Lin , Gastroenterology 1988	63
GRETCH, NEJM 1995	96
Bruix , Hepatology 1998	80
Pelletier, J Hepatol 1998	70
Lo, Hepatology 2002	79
Llovet, Lancet 2002	112
Overall	503

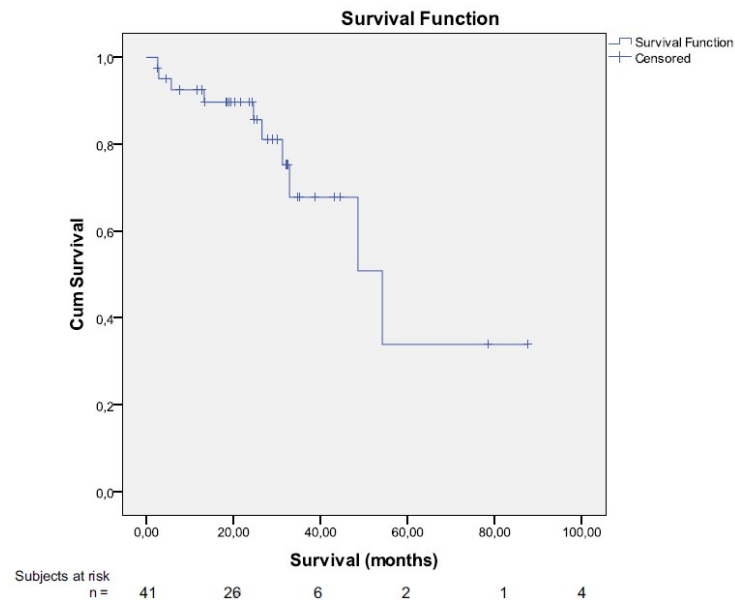
Heterogeneity: Q:7.73 P=0.14

Improved survival: from 16 to 20 months

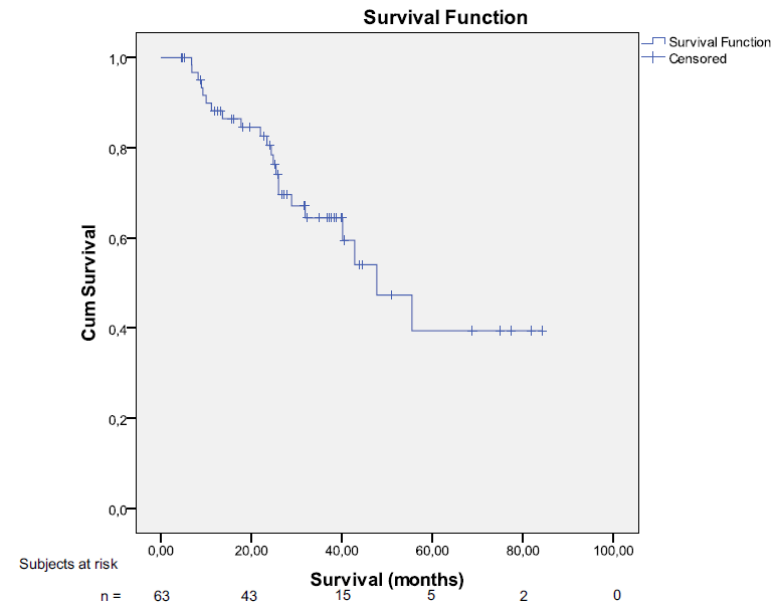


Survival of Patients with Hepatocellular Carcinoma Treated by TACE Using DC-beads

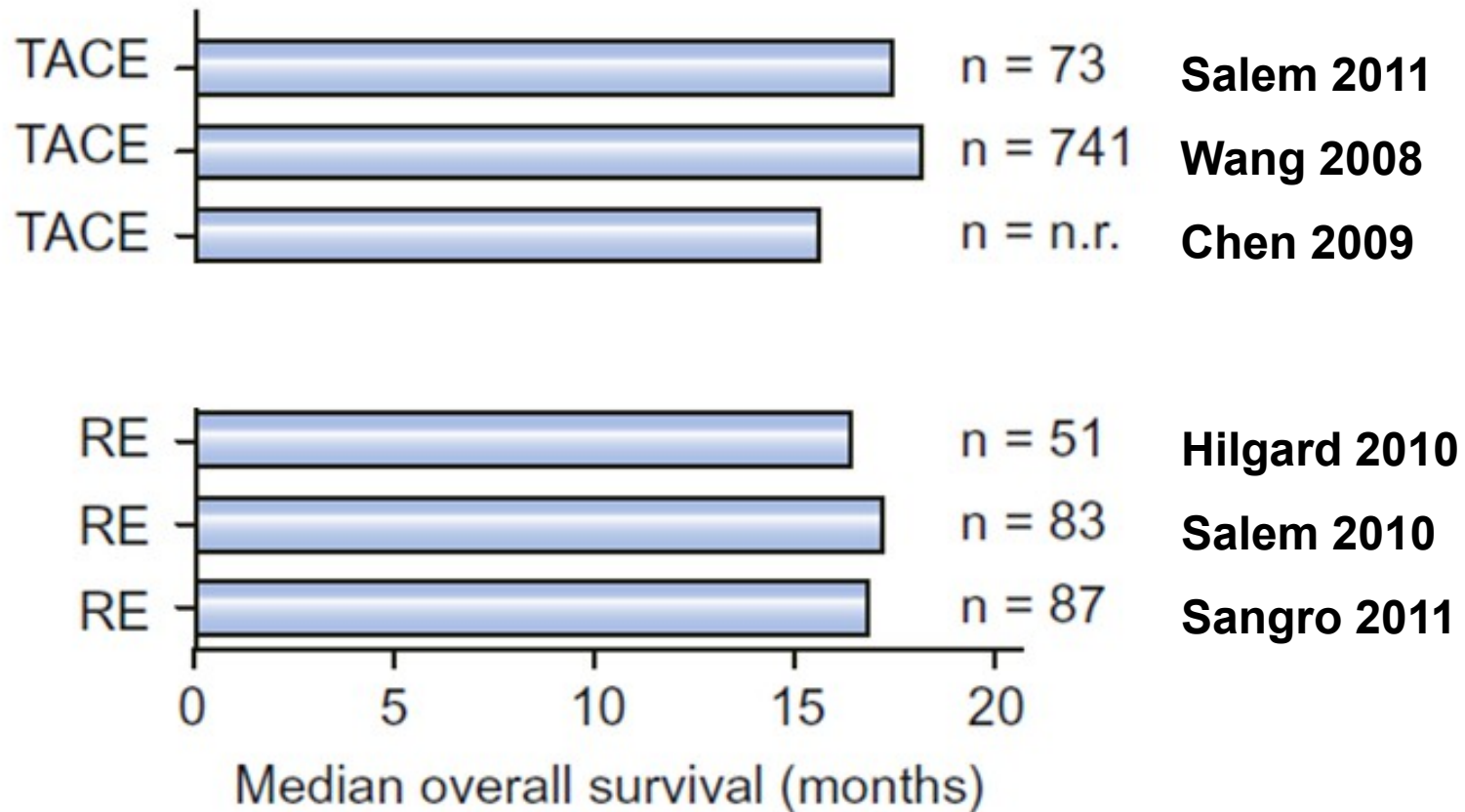
Overall survival BCLC-A



Overall survival BCLC-B

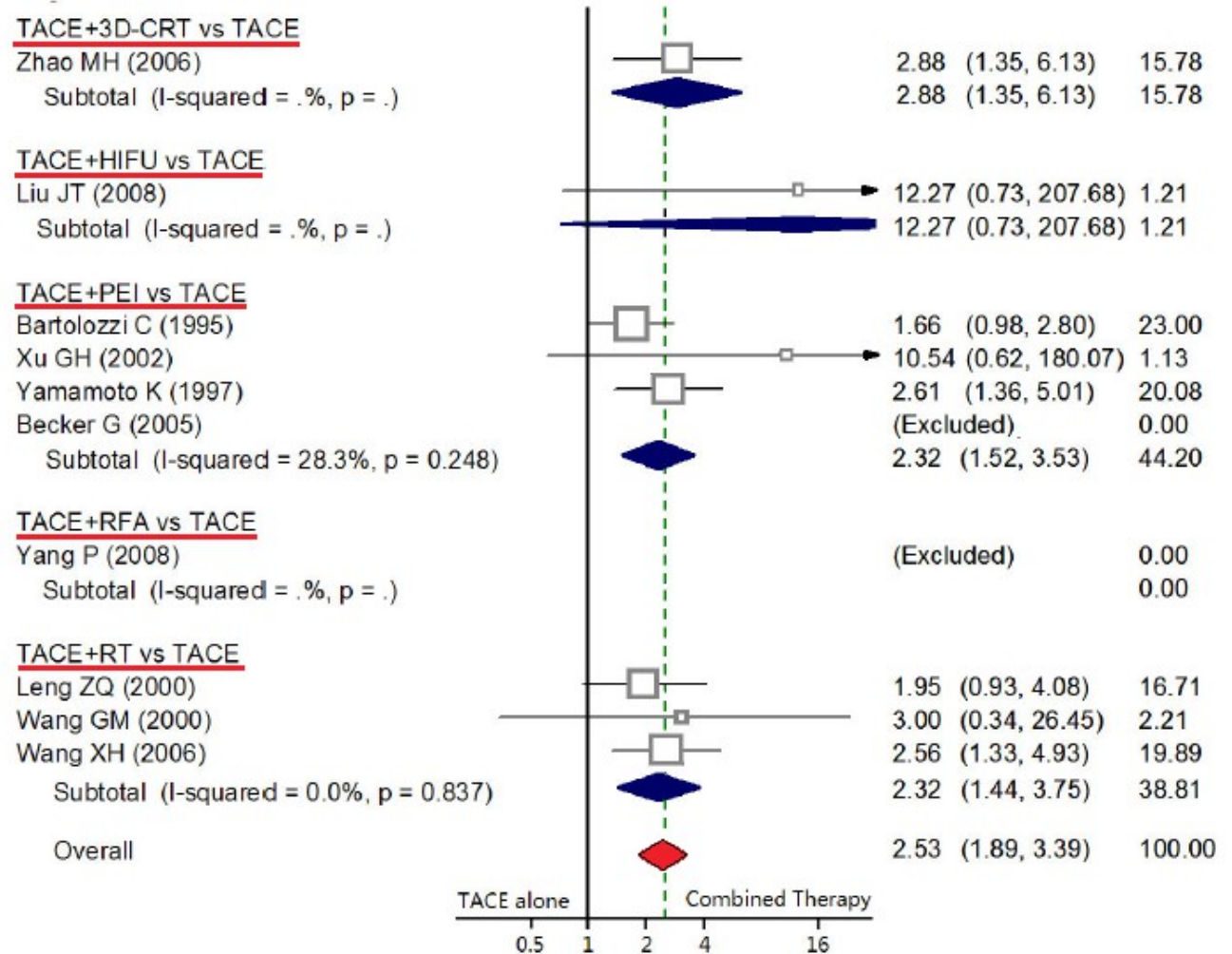


Uncontrolled Studies: Y-90 Radioembolization (RE) in BCLC B Patients



Transarterial Chemoembolization in Combination with Local Therapies for HCC: A Meta-Analysis

Three-yr survival



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Randomized Controlled Trials of Sorafenib in Advanced Hepatocellular Carcinoma

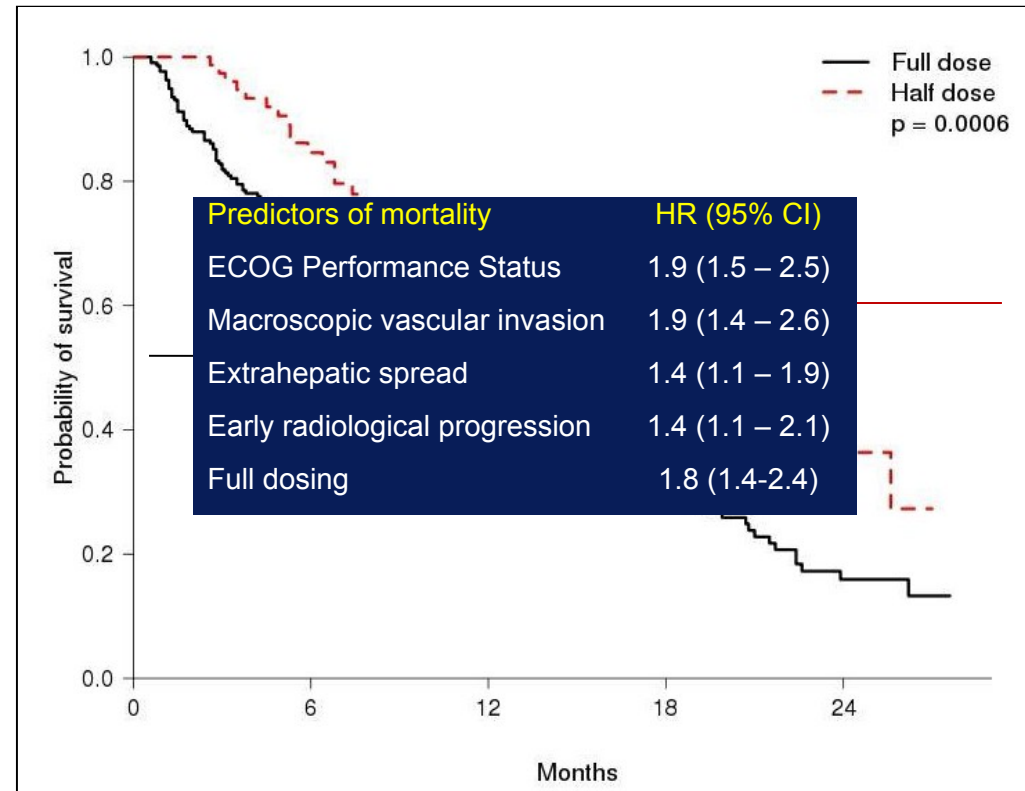
Study Characteristics	SHARP Study ¹	Asia Study ²
Median age	65 yrs	51 yrs
BCLC-B stage	18%	4%
Previous treatments	67%	na
HBV etiology of cirrhosis	19%	71%
<u>TTP (control)</u>	5.5 mo (2.8 mo)	2.8 mo (1.4 mo)
<u>Median survival (control)</u>	10.7 mo (7.9 mo)	6.5 mo (4.2 mo)
Grade 3/4 toxicity	30%	24%

1. Llovet JM, et al. *N Eng J Med.* 2008;359(4):378-390; 2. Cheng A et al. *Lancet Oncol.* 2009;10(1):25-34.

Overall Survival According to the Prevalent Dose of Sorafenib in the SOFIA Study (296 Patients)

Total patients: 296

- 97 (40%) discontinued without previous dose reduction
- 122 with half dose for <70% of the treatment period
- 77 patients with half dose for ≥70% of the treatment period

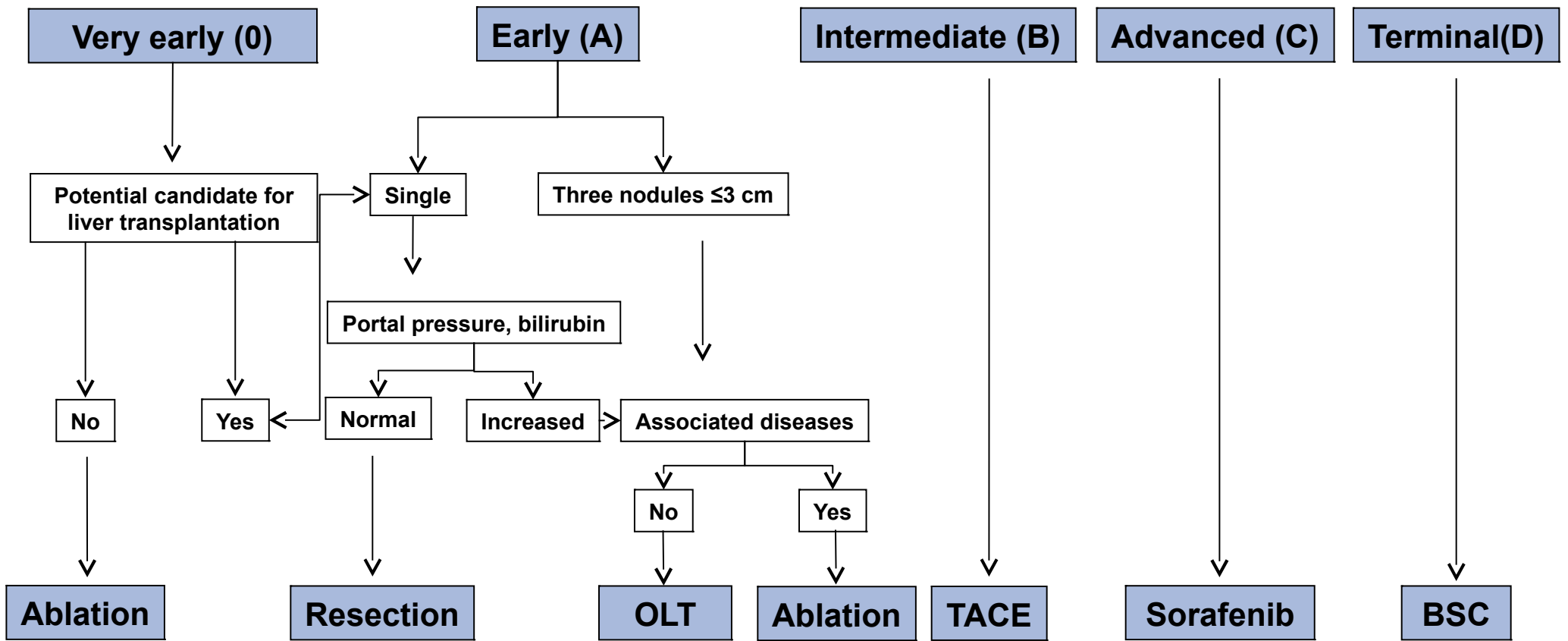


OS in Phase 3 Trials in Patients with Advanced HCC

1st and 2nd Line

Study	Year	Drug	n.	OS (mo)	P-value	Hazard ratio (95%CI)
First Line						
Zhu et al	2012	Sorafenib + erlotinib vs. sorafenib + placebo	362/358	9.5 vs. 8.5	n.s.	0.92 (0.78-1.11)
Cainap et al	2012	Linifanib vs. sorafenib	514/521	9.1 vs. 9.8	n.s.	1.04 (0.89-1.22)
Cheng et al	2013	Sunitinib vs. sorafenib	530/544	7.9 vs. 10.2	n.s.	1.30 (1.13-1.50)
Johnson et al	2013	Brivanib vs. sorafenib	577/578	9.5 vs. 9.9	n.s.	1.07 (0.94-1.23)
Qin et al	2013	FOLFOX-4 vs. doxorubicin	184/187	6.4 vs. 4.9	n.s.	0.80 (0.63-1.02)
Second Line						
Llovet et al	2013	Brivanib vs. placebo	263/132	9.4 vs. 8.2	n.s.	0.89 (0.69-1.15)
Zhu et al	2014	Everolimus vs. placebo	362/184	7.6 vs. 7.3	n.s.	1.05 (0.86-1.27)

The Founders of BCLC: Staging and Treatment Strategy



Association of Multidisciplinary (MDC) HCC Clinic with Clinical Outcome



105 patients diagnosed after the MDC clinic (2010)
vs
209 patients diagnosed in the 3 previous years

1. Received treatment	56% vs 44%	P=0.04
2. Time to treatment (mo.)	2.2 vs 4.7	P=0.001
3. Survival time (mo.)	15.2 vs 4.7	P=0.002
4. One-year survival	64% vs 47%	P=0.001*

*after excluding BCLC-D patients