



ASIAN PACIFIC ASSOCIATION FOR THE STUDY OF THE LIVER

in cooperation with

HEPATOLOGY SOCIETY OF THE PHILIPPINES



3RD APASL SINGLE TOPIC CONFERENCE

HCC IN 3D

November 21-23, 2013 Radisson Blu Hotel Cebu City, Philippines



SIRT for Intermediate and Advanced HCC

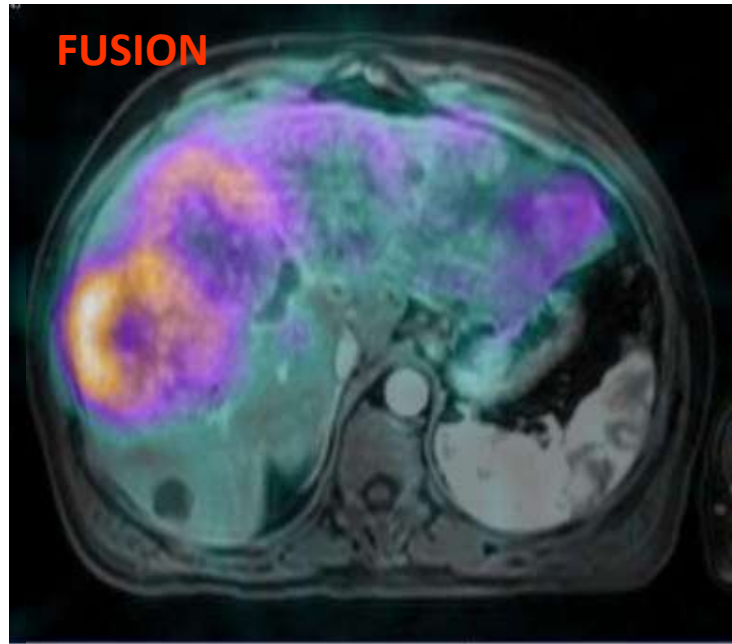
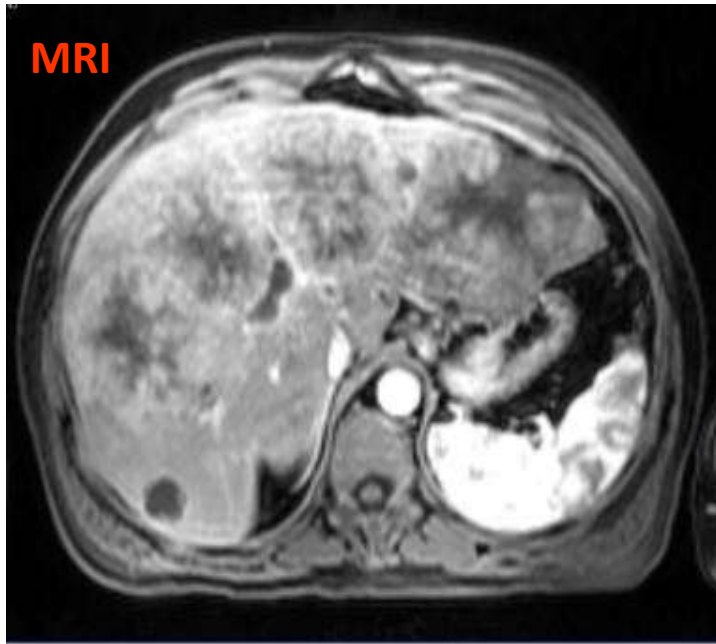
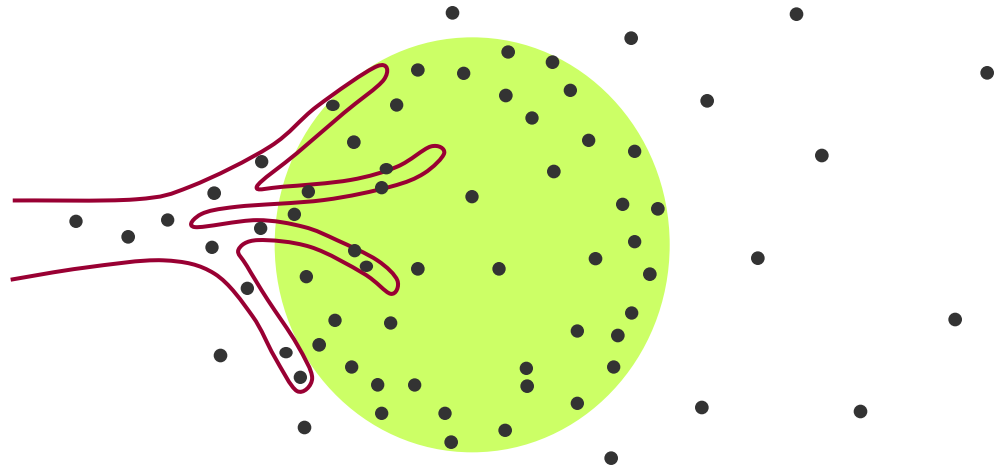
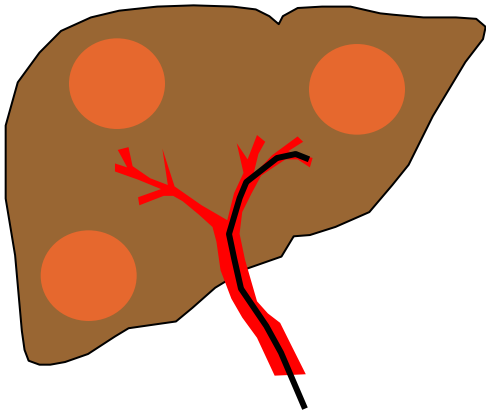


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Pamplona, Spain



^{90}Y -RE

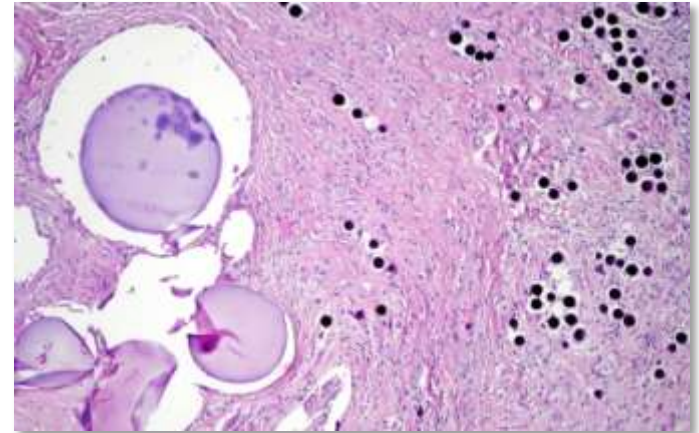


^{90}Y -RE = Yttrium-90 radioembolization

Sangro B. Personal communication.

Microspheres for ^{90}Y -RE

	Resin	Glass
Mean diameter	32.5 μm	25 μm
Activity/sphere	50 Bq	2,500 Bq



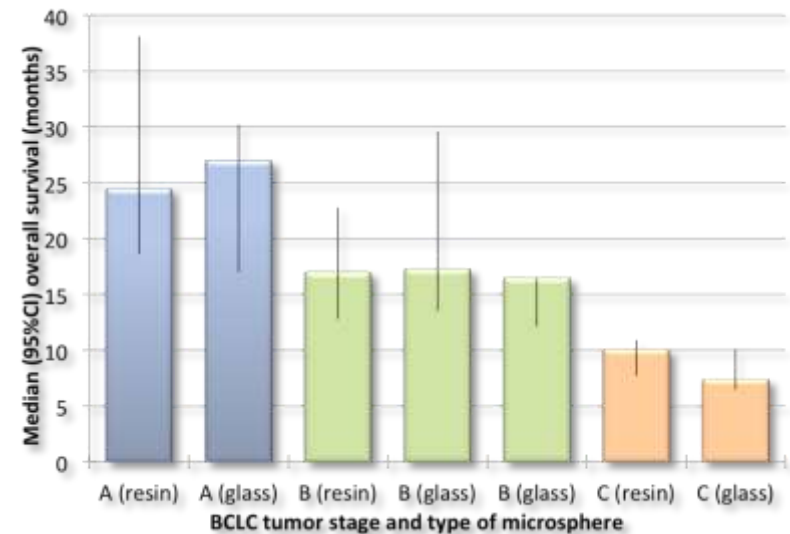
Source of radiation: Yttrium-90

Pure **beta** emitter

Mean **penetration: 2.5 mm**

Half-life: 64.2 h

- **95% of dose delivered by Day 11**



1. Salem R, et al. Gastroenterology. 2010;138:52–64

2. Hilgard P, et al. Hepatology. 2010;52:1741–9;

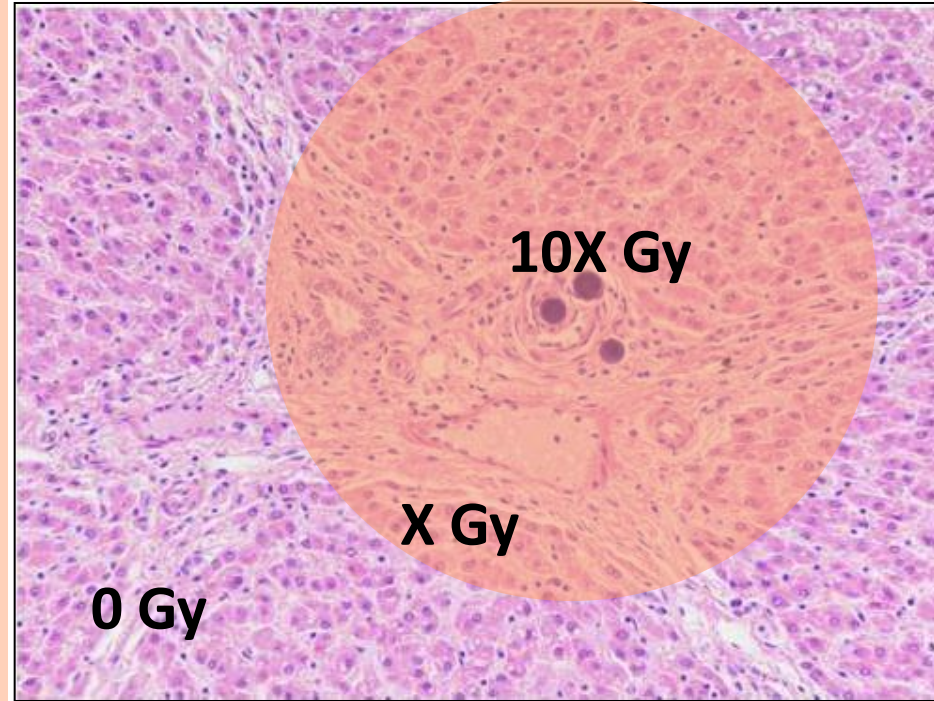
3. Sangro B, et al. Hepatology. 2011;54:868–78

Dosimetry and radiobiology of ^{90}Y -RE

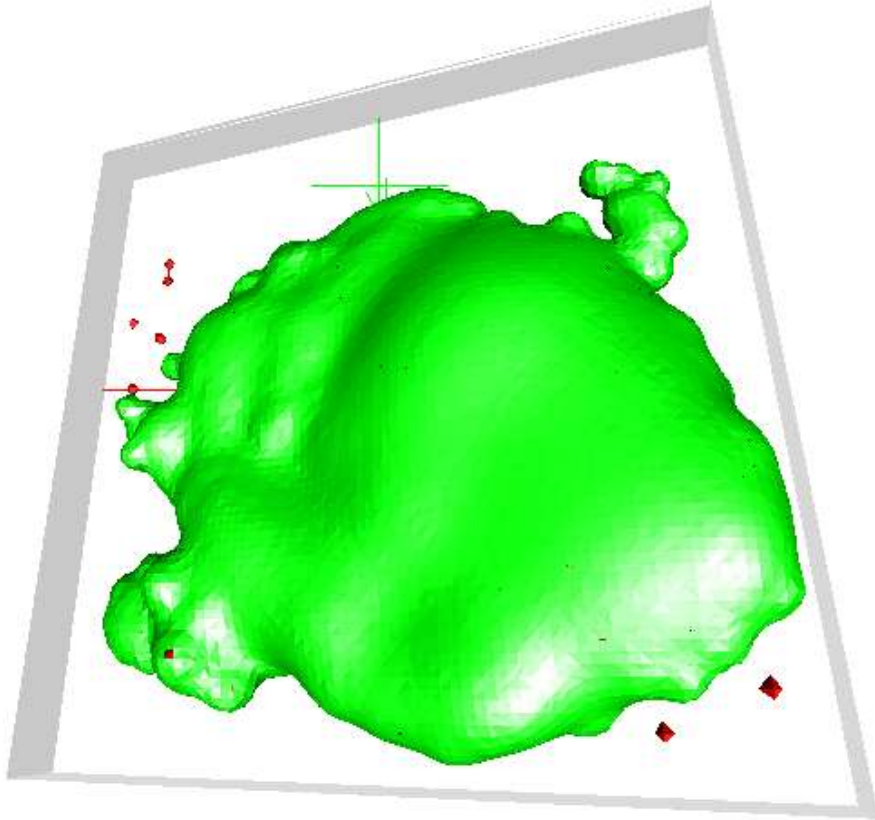
External beam radiation



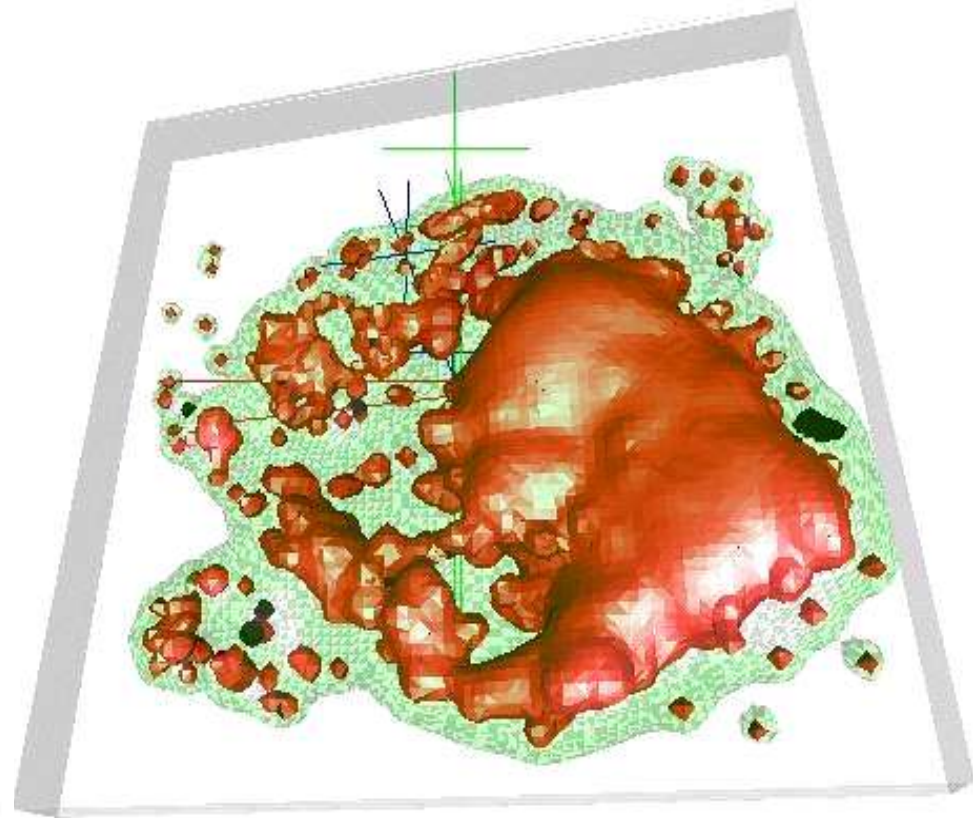
Internal radiation



Microsphere distribution and absorbed radiation dose in humans



100 Gy dose volume



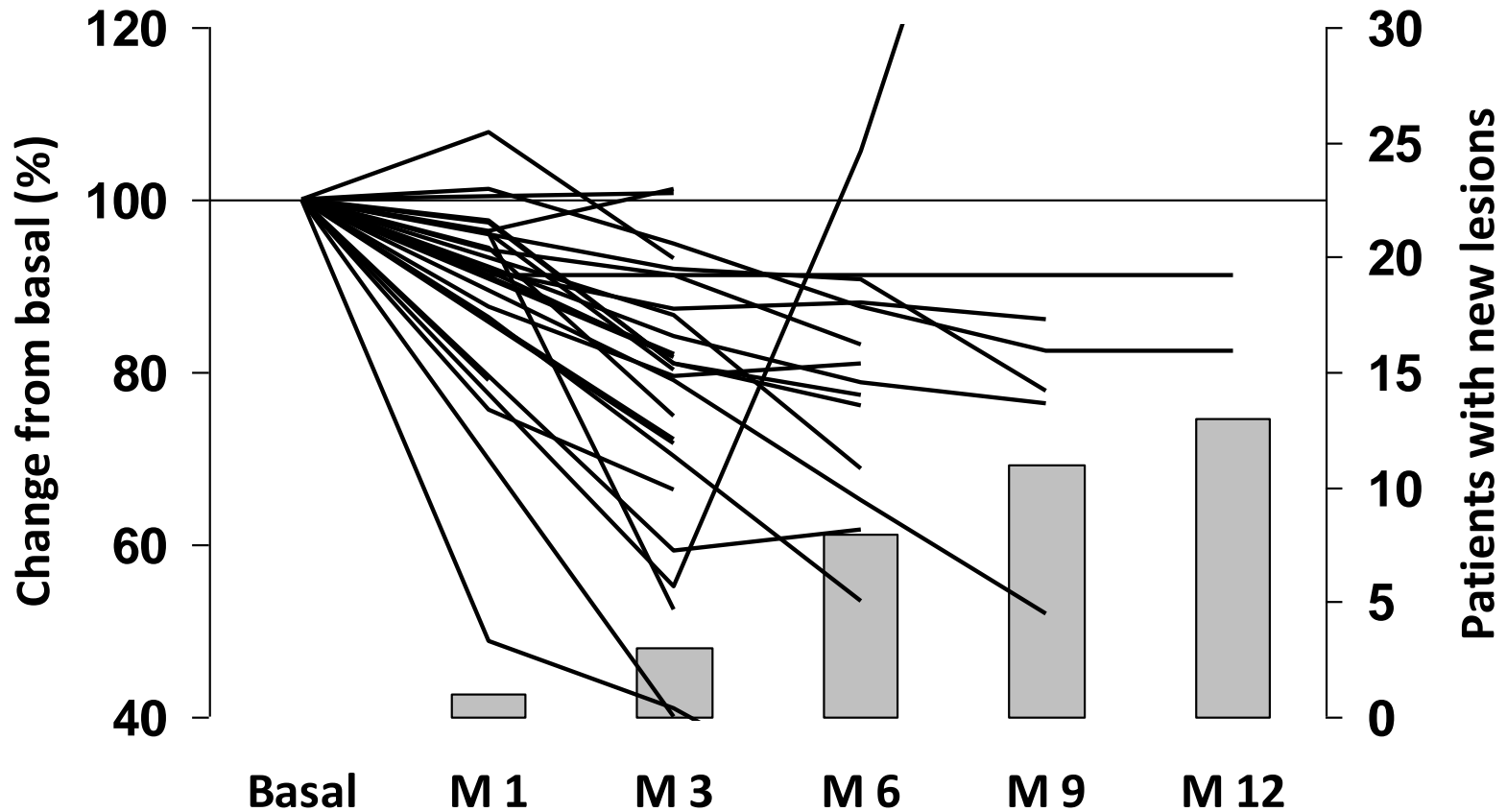
1000 Gy dose volume

RE in HCC

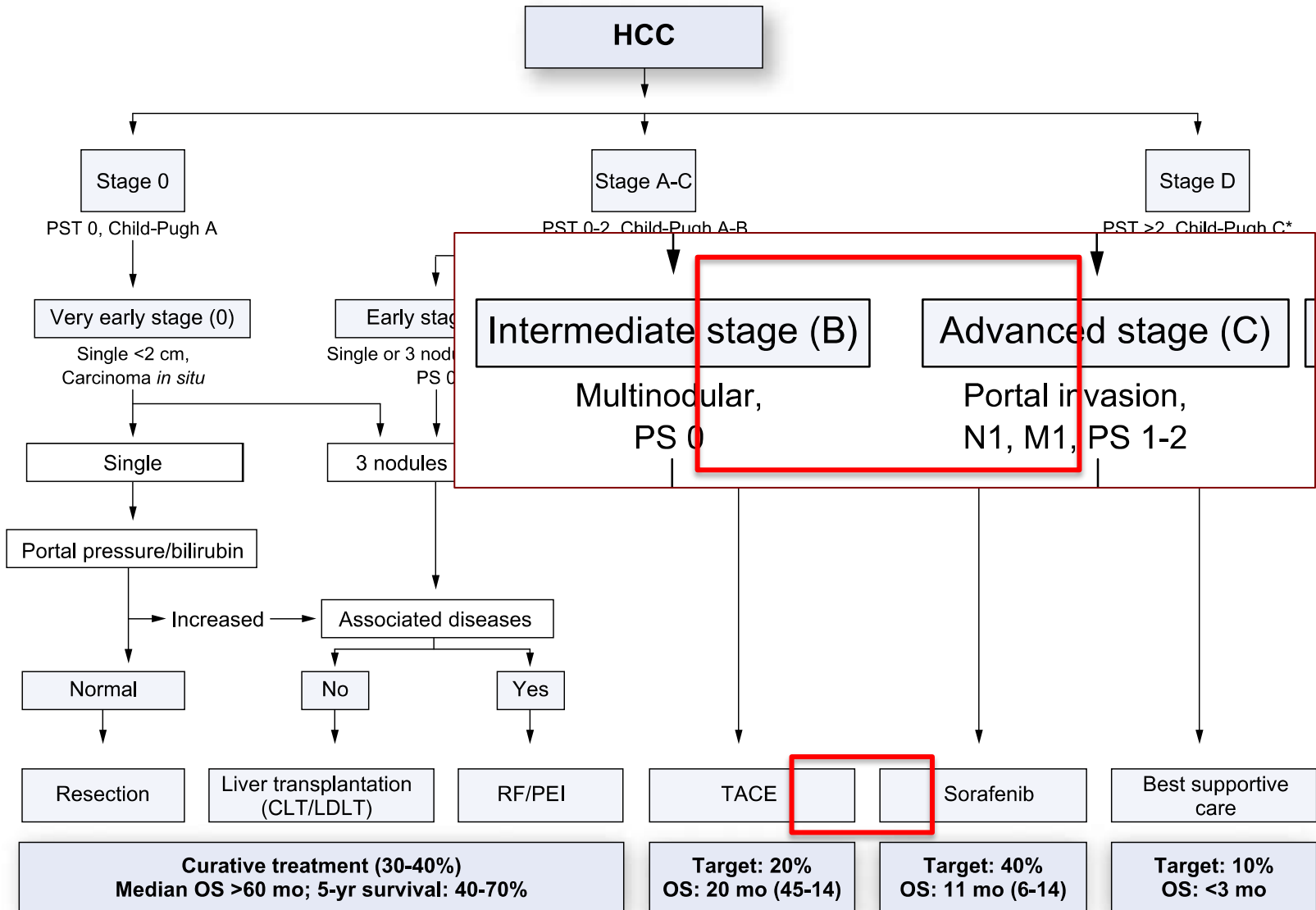
Sum of maximal diameters of target lesions (RECIST)
30 evaluable patients

Disease control rate: 78%

Response rate: 21%



BCLC staging system

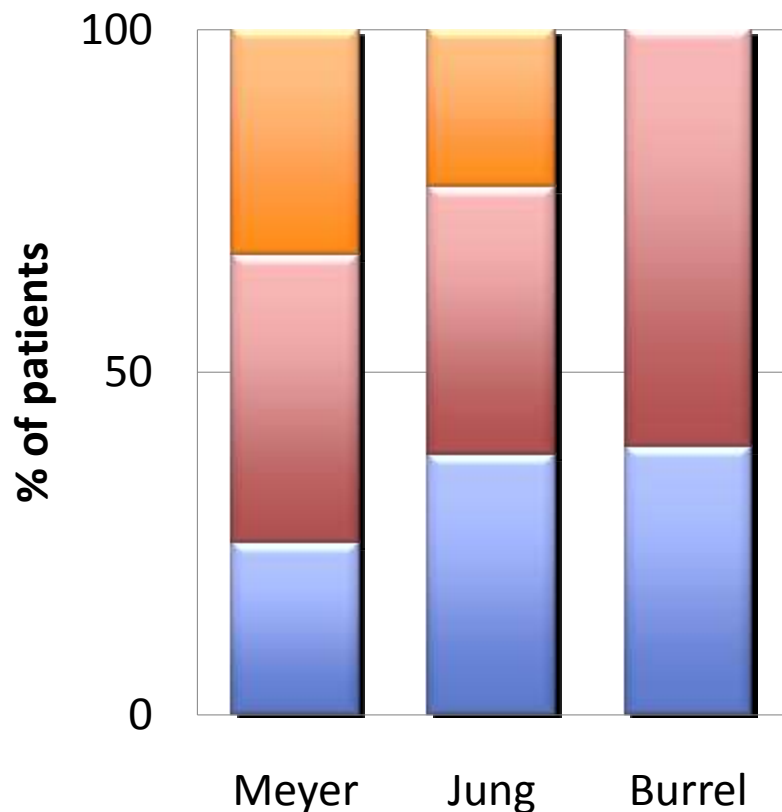


TACE and RE in Clinical Practice

Patient Profiles (BCLC Stages)

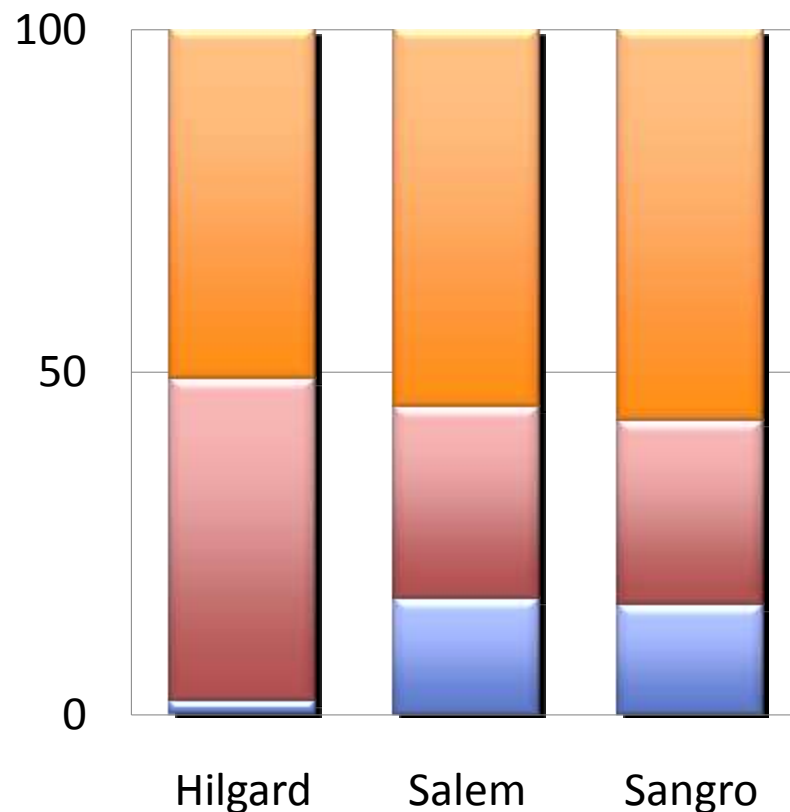
TACE

■ Early ■ Intermediate ■ Advanced



RE

■ Early ■ Intermediate ■ Advanced



Burrel M, et al. J Hepatol. 2012; 56:1330.
Jung ES, et al. J Hepatol. 2013. 58:1181-1187.
Meyer T, et al. Br J Cancer 2013.

Sangro B, et al. Hepatology. 2011;54:868-78
Salem R, et al. Gastroenterology. 2010;138:52-64
Hilgard P, et al. Hepatology. 2010;52:1741-9

Time to Progression after TACE and RE

Patients in the Intermediate Stage

Treatment	RE ¹	RE ²	cTACE ³	DEB-TACE ⁴
No. of patients	65	17	31	153
Response criteria	EASL	EASL	Other	mRECIST
Median TTP (mo)	13.3	13	4.9	5.5
95% CI for TTP (mo)	8.4–25.9	6–nc	1.6–7.5	3.7–5.6

1. Salem R, et al. Gastroenterology. 2011;140:497–507; 2. Mazzaferro V, et al. Hepatology 2013;57:1826-37.
3. Sansonno D, et al. Oncologist. 2012;17:359–66; 4. Lencioni R, et al. Presented at ASCO GI 2012. Abstract LBA154.

Overall Survival after TACE and ⁹⁰Y-RE

245 patients treated in a single Center. Treatment allocation by MDT

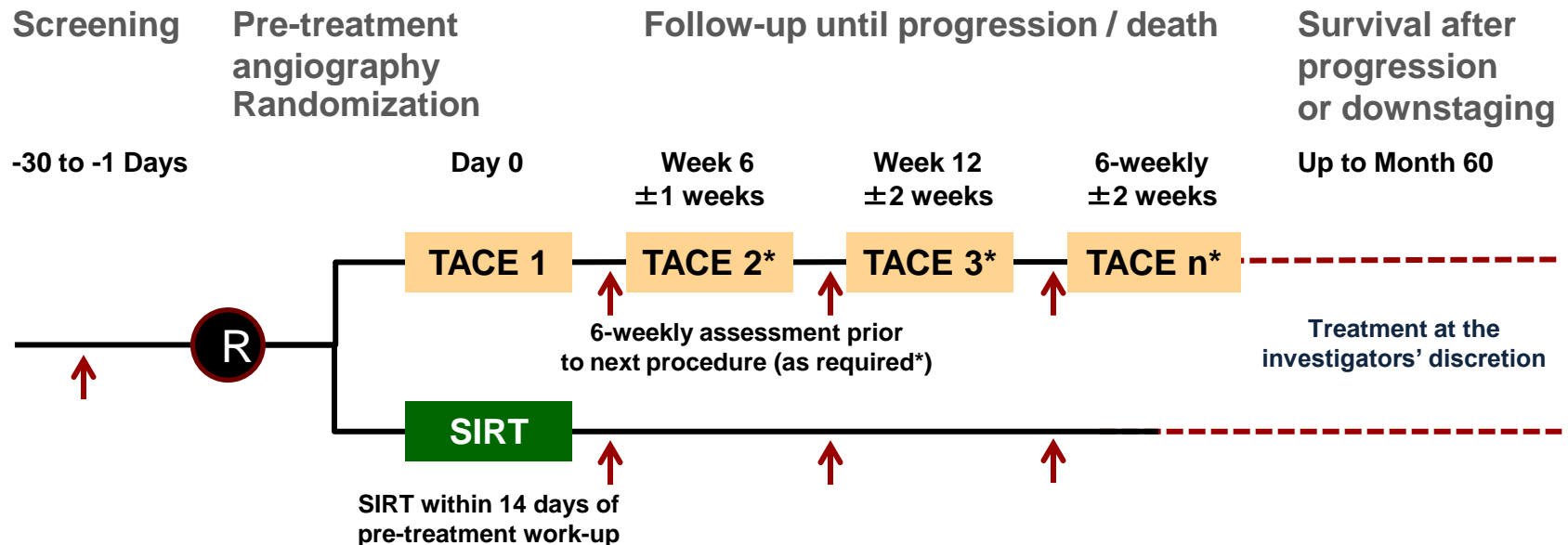
BCLC stage	TACE (n=122)	Y90 (n=123)	P	Adj p*
A	45.4 (15.1-46.1)	27.3 (17.1-30.2)	0.74	
B	17.5 (14.8-18.7)	17.2 (11.4-29.6)	0.42	
C	9.3 (6.2-11.5)	22.1 (11.2.-)	0.04	0.08

* p value adjusted for multiple comparisons (correction factor =2)

SIRTACE Trial

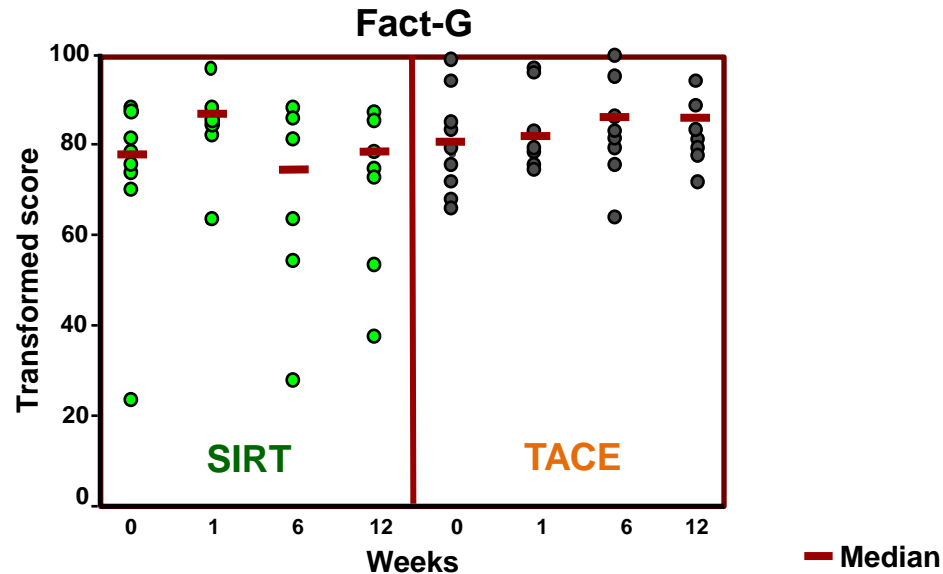
Study Design

- Pilot, open-label, randomised, prospective, cohort comparison conducted at two European centres:
 - University of Munich, Germany and Clinica Universidad de Navarra, Spain
- A sample size of 28 evaluable patients was chosen to allow the detection of a difference in HRQoL between the two treatments



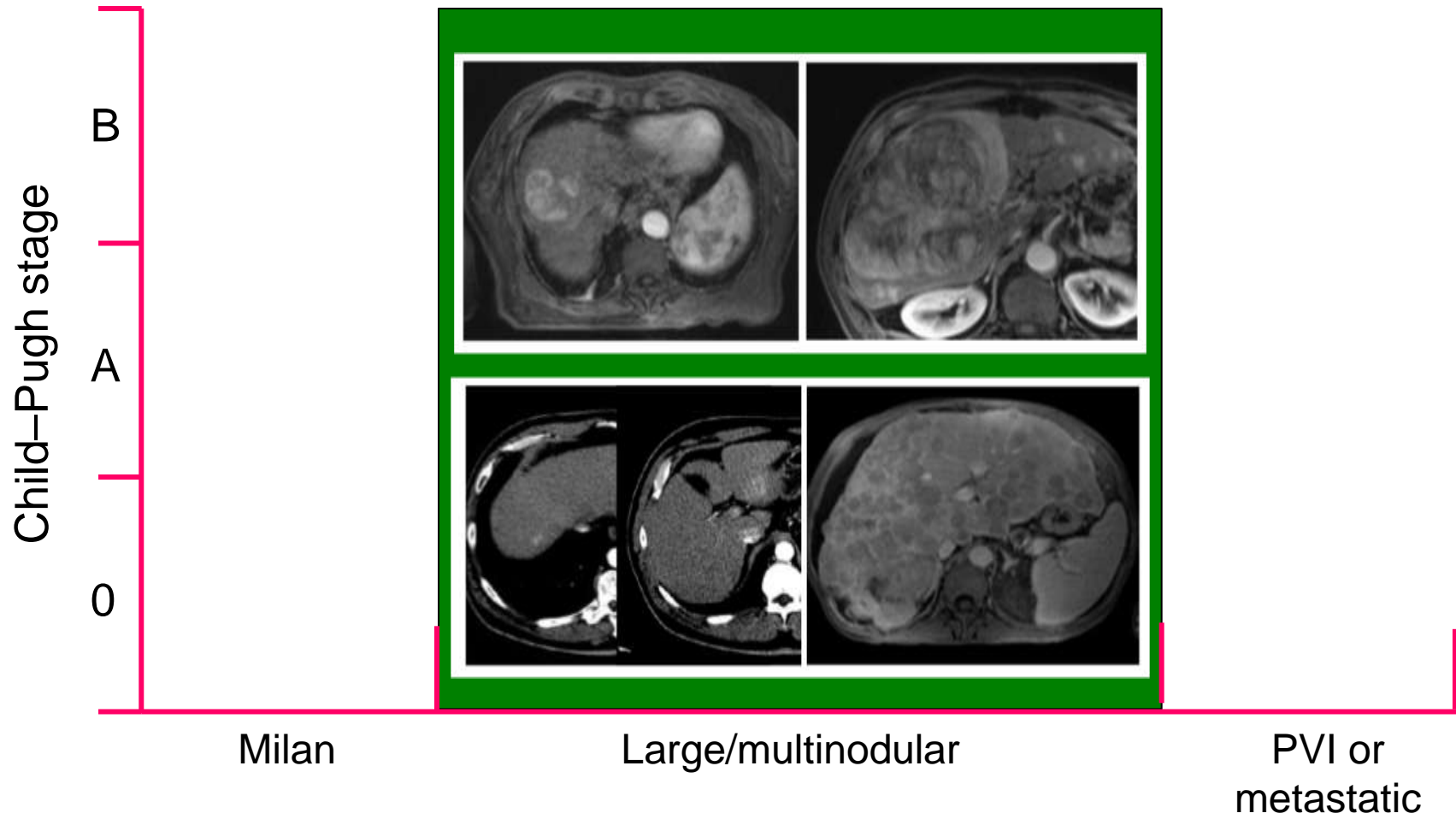
SIRTACE Trial

Health-Related Quality of Life



Progression-free survival and overall survival did not differ by procedure ($p=0.374$ and $p=0.244$, respectively)

The Intermediate Stage



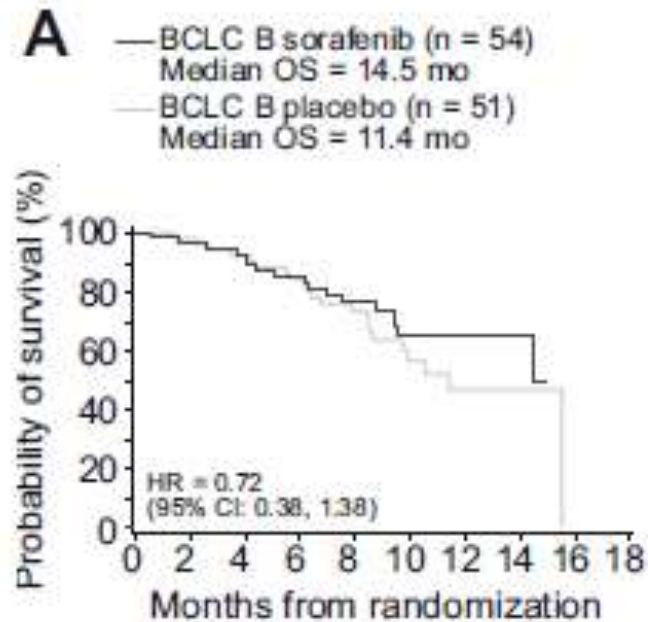
Suggested contraindications to TACE in intermediate-stage HCC

Absolute contraindications	Relative contraindication
Decompensated cirrhosis (Child–Pugh B \geq 8): <ul style="list-style-type: none"> • Jaundice • Encephalopathy • Refractory ascites • Hepatorenal syndrome 	Comorbidities with clinically significant compromised organ function
Extensive tumour with massive replacement of both entire lobes	Tumour size \geq 10 cm
Severely reduced portal vein flow	Ascites at high risk of bleeding
Technical contraindications to TACE (e.g. untreatable AV fistula)	Vessel occlusion or incompetent portal vein or stent or surgery
Renal insufficiency (creatinine $>$ 2.5 mg/dL or creatinine clearance $<$ 30 mL/min)	

Consider alternatives

Sorafenib in the Intermediate Stage HCC

SHARP



however, the wide confidence interval for OS in the BCLC B subgroup did not allow a robust conclusion in these patients.

Refinement of BCLC classification

- A panel of experts acknowledges that the range of survival reported for patients at BCLC-B (11–45 months) and C (5–11 months) deserves to be addressed
- Further stratification of patients within each class according to liver function (Child–Pugh A vs B, or ascites), prognostic molecular biomarkers or prognostic variables (ECOG, cancer invasiveness) should be explored

Treatment options in intermediate-stage HCC

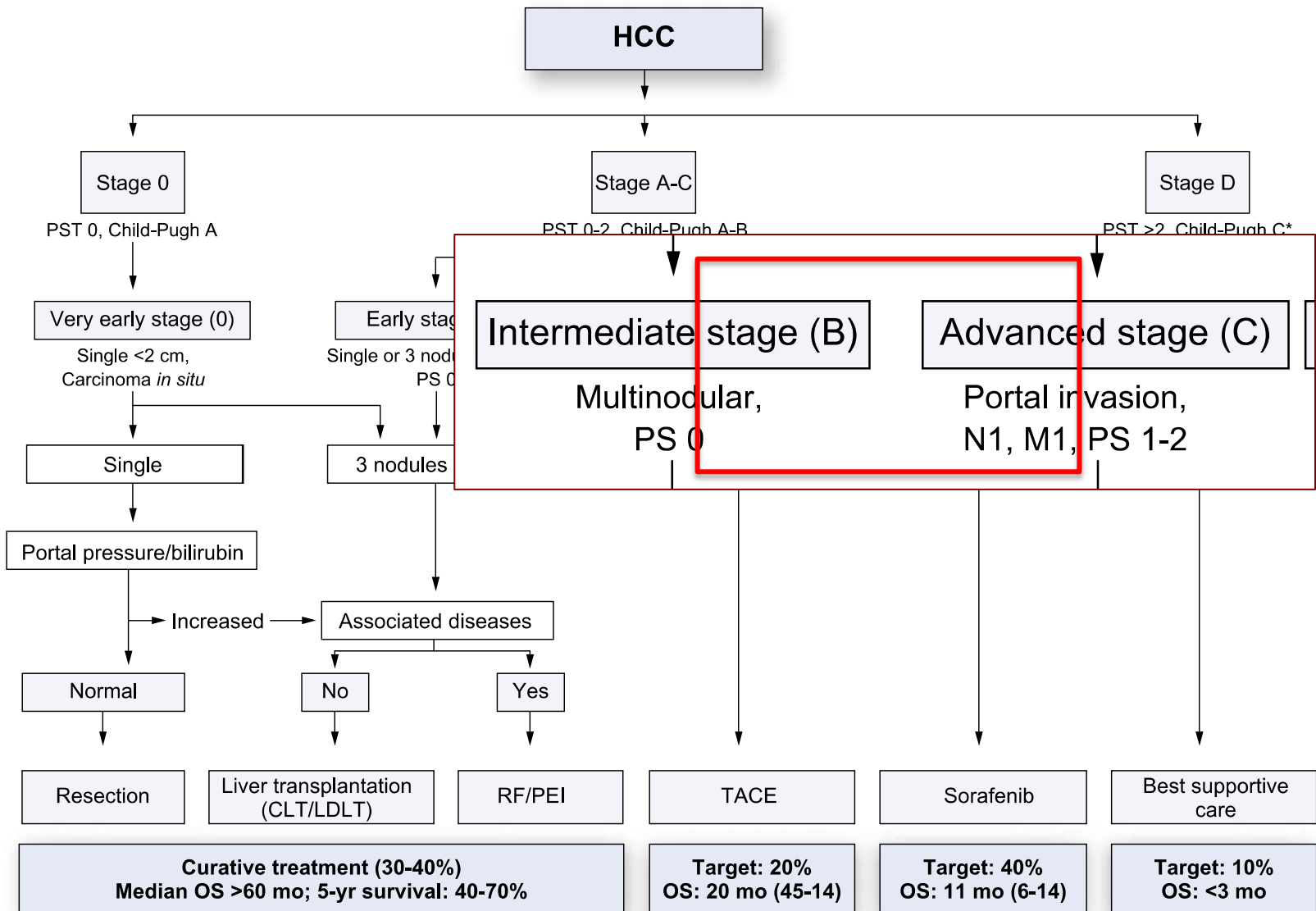
An expert opinion consensus

BCLC substage	B1	B2	B3	B4
Beyond Milan Within Up-to-7	IN	OUT	OUT	ANY
CPT score	5–6–7	5–6	7	8–9*
ECOG PS	0	0	0	0–1
PVT	NO	NO	NO	NO
1st treatment option	TACE	TACE or TARE		BSC
Alternative treatment	LT or TACE + ABL	SOR	Research or TACE	LT**

*With severe/refractory ascites and/or jaundice; **Only if up-to-7 IN and PS 0; **Bold** options are supported by highest scientific evidence.

% of pts	41%	35%	7%	17%
mOS (mo)	34	24	15	12

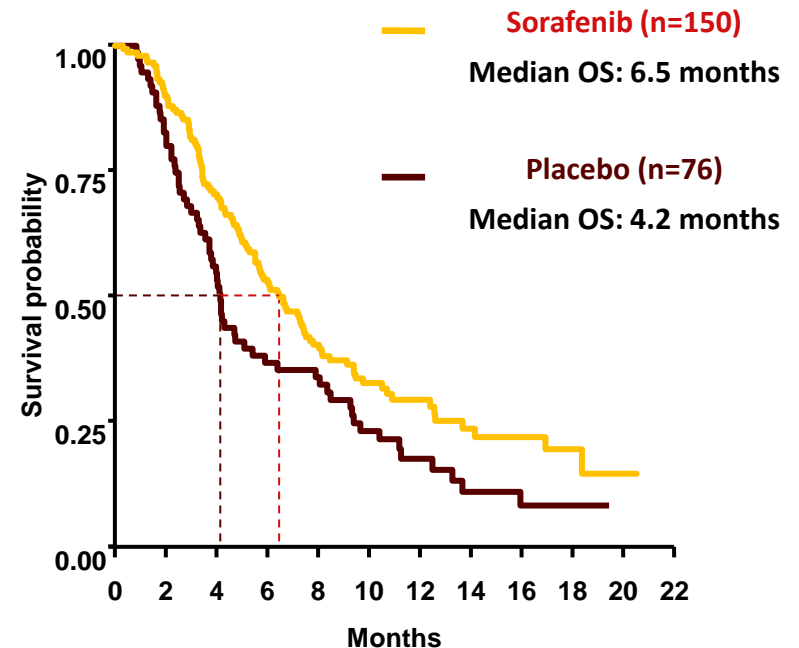
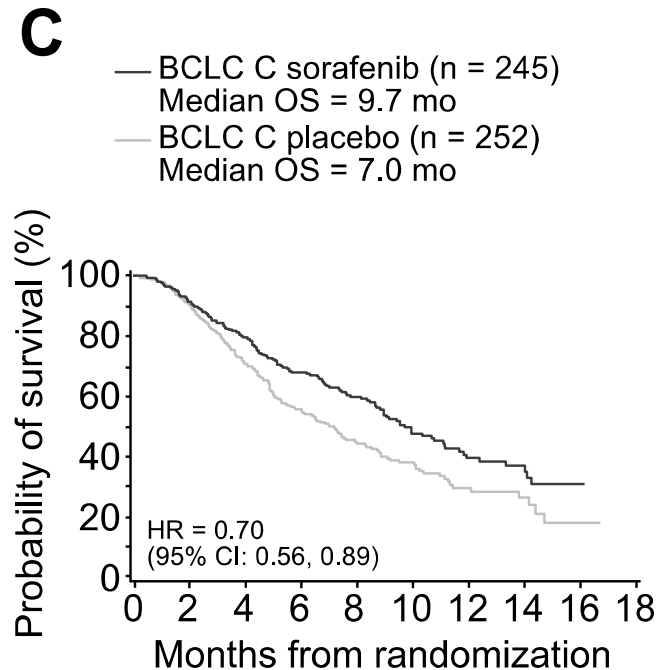
BCLC staging system



Sorafenib for Advanced Stage Patients

SHARP

Asia-Pacific

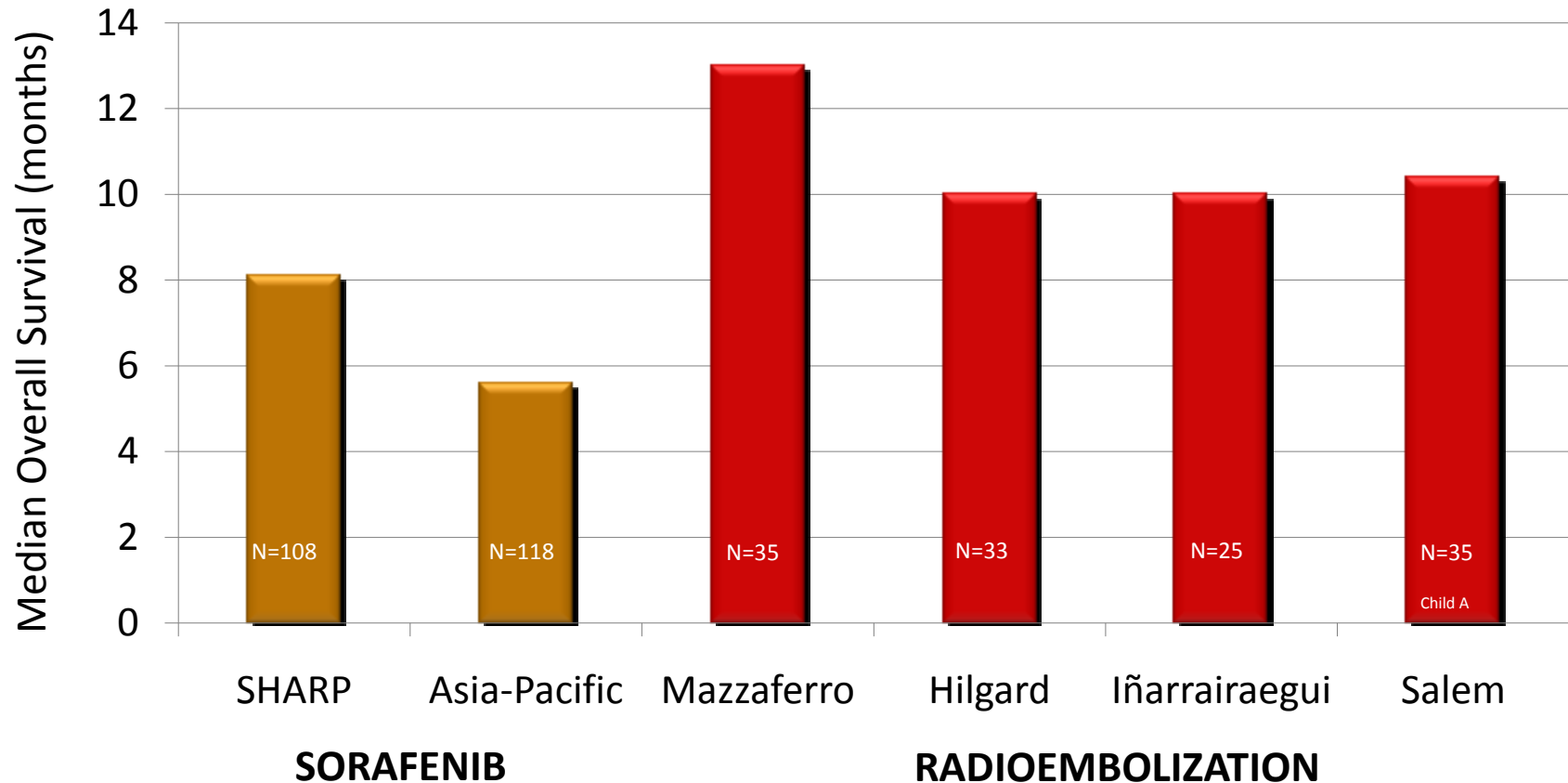


Sorafenib for Stage C Patients with PVT

Subgroup domain	Group evaluated	Number of patients		OS (mo)		
		Sor	PI	Sor	PI	HR (95% CI)
-	SHARP overall population ^a	299	303	10.7	7.9	0.69 (0.55-0.87)
	Subgroup					
Etiology of HCC	Positive for anti-HCV antibody	86	81	14.0	7.4	0.50 (0.32-0.77)
	Positive for HBsAg	32	28	9.7	6.1	0.76 (0.38-1.50)

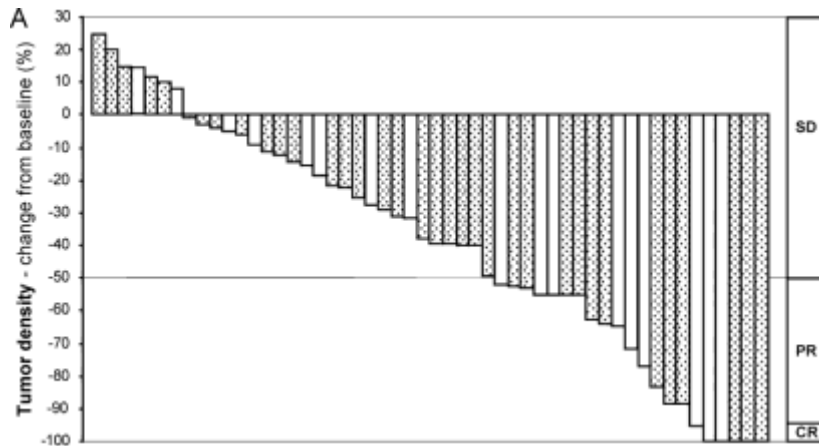
Group evaluated	Number of patients		OS (mo)			
	Sor	PI	Sor	PI	HR (95% CI)	
MVI present	108	123	8.1	4.9	0.68 (0.49-0.93)	
	EHS absent	140	153	14.1	7.9	0.55 (0.39-0.77)
	EHS present	159	150	8.9	8.3	0.85 (0.64-1.15)
Performance status	ECOG PS 0	161	164	13.3	8.8	0.68 (0.50-0.95)
	ECOG PS 1-2	138	139	8.9	5.6	0.71 (0.52-0.96)
Tumor stage	BCLC B	54	51	14.5	11.4	0.72 (0.38-1.38)
	BCLC C*	245	252	9.7	7.0	0.70 (0.56-0.89)
Prior therapy	Prior curative treatment [†]	81	77	11.9	8.8	0.79 (0.51-1.22)
	Prior TACE	86	90	11.9	9.9	0.75 (0.49-1.14)

Median Survival In Advanced Stage Patients With Portal Vein Thrombosis



Hilgard, et al. *Hepatology*. 2010;52:1741-9. Salem, et al. *Gastroenterology*. 2010;138:52-64
Cheng, et al. *Eur J Cancer*. 2012;48:1452-65. Bruix, et al. *J Hepatol*. 2012;57:821-9.
Mazzaferro, et al. *Hepatology*. 2013;57:1826-37. Iñarrairaegui M, et al. *J Vasc Interv Radiol*. 2010;21:1205-12

RE for Advanced Stage Patients with PVT



Median TTP: 11 months (95%CI: 6-11)
PVT absent: 13 months (95%CI: 6-n.c.)
PVT present: 7 months (95%CI: 6-12)

Tumor response by EASL criteria

PVT patients (dotted bars):

Objective response: 37%

Disease control: 74%

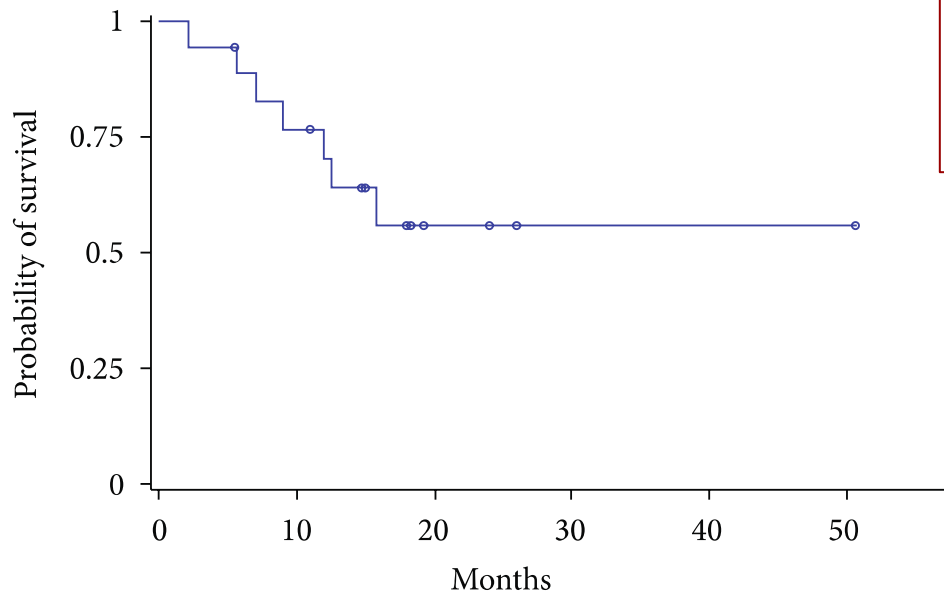
3-year Survival

Responders: 25%

Non-responders: 4.4%

RE for Advanced Stage Patients with PVT

- 18 patients with branch (10) or main (8) PVT
- Child A (13) or B7 (5)
- Unifocal (8), multifocal (7) or diffuse (3) tumors
- Median size: 8.7 cm (range 3-13)



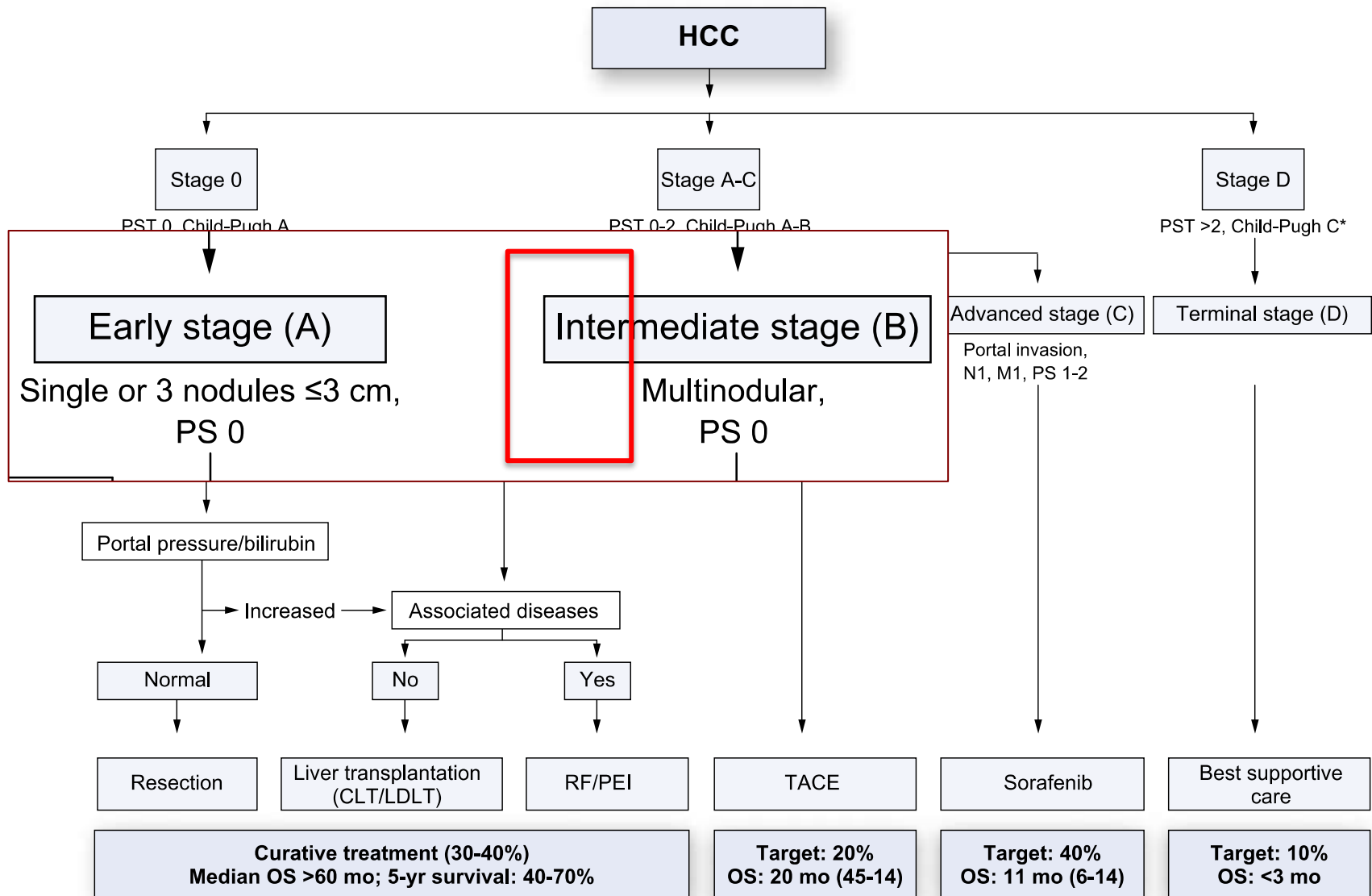
Response rate: 83%

Median TTP: 11 months (95%CI 8-16.5)

Median OS: not reached (95%CI 9- ∞)

OS at 1 year: 70%

BCLC staging system



DOWNSTAGING

EARLY
TUMOR



CURATIVE
THERAPY



GOOD
OUTCOME



STABLE TUMOR RESPONSE



INTERMEDIATE
TUMOR



PALLIATIVE
THERAPY



INTERMEDIATE
OUTCOME

DOWNSTAGING

EARLY
TUMOR



CURATIVE
THERAPY

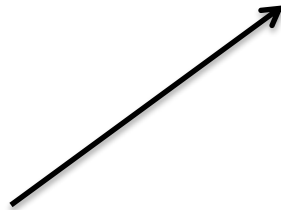


GOOD
OUTCOME

TRANSPLANT

ABLATION

RESECTION



TUMOR
SHRINKAGE

INCREASED
LIVER REMNANT



INTERMEDIATE
TUMOR



PALLIATIVE
THERAPY



INTERMEDIATE
OUTCOME

DOWNSTAGING

EARLY
TUMOR



CURATIVE
THERAPY

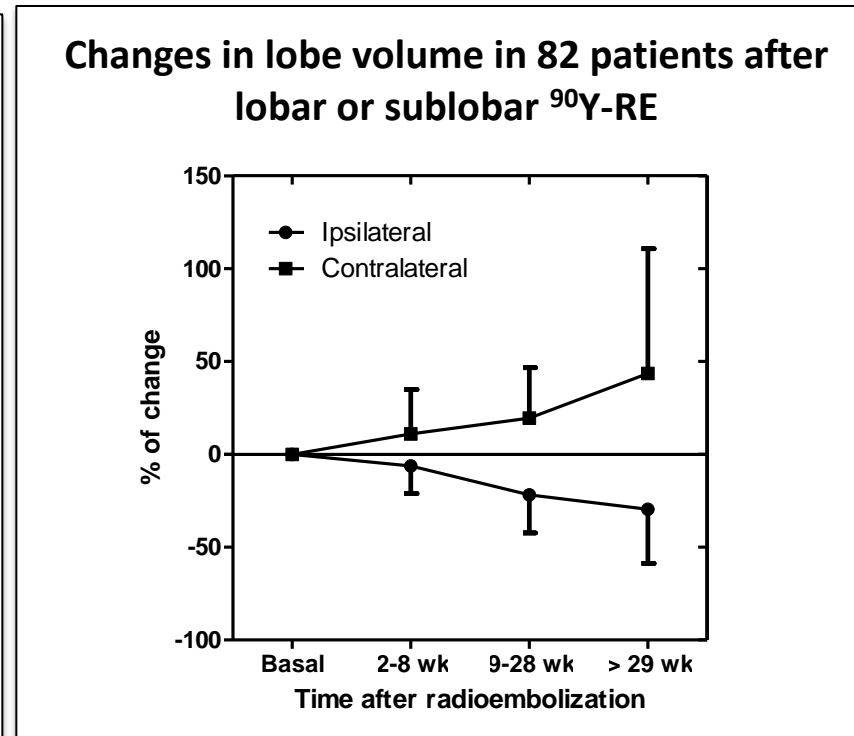
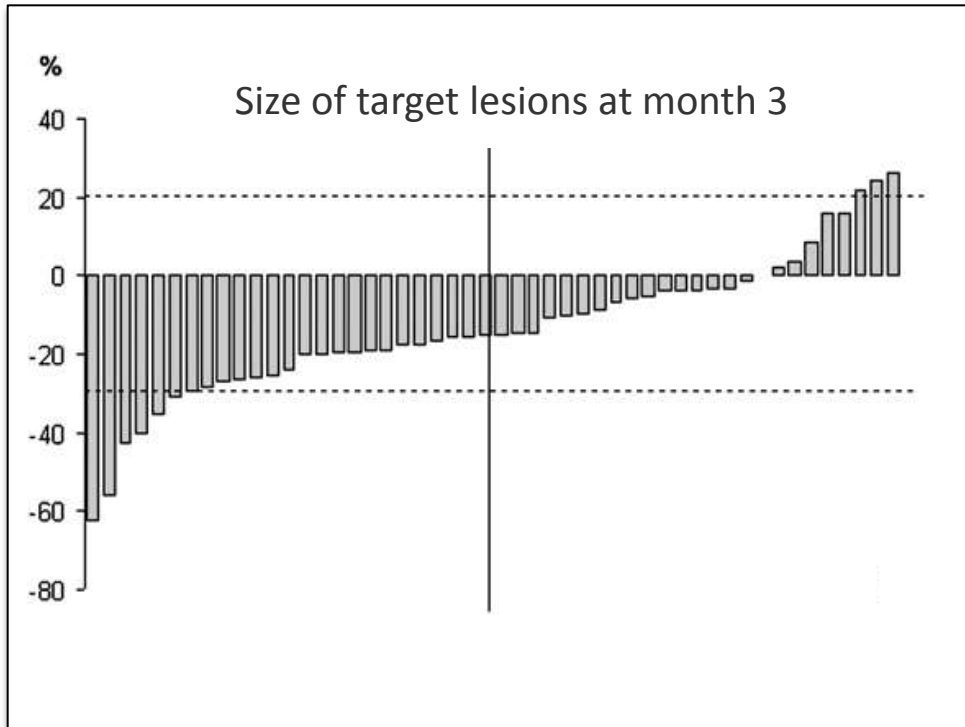


GOOD
OUTCOME

TRANSPLANT

ABLATION

RESECTION

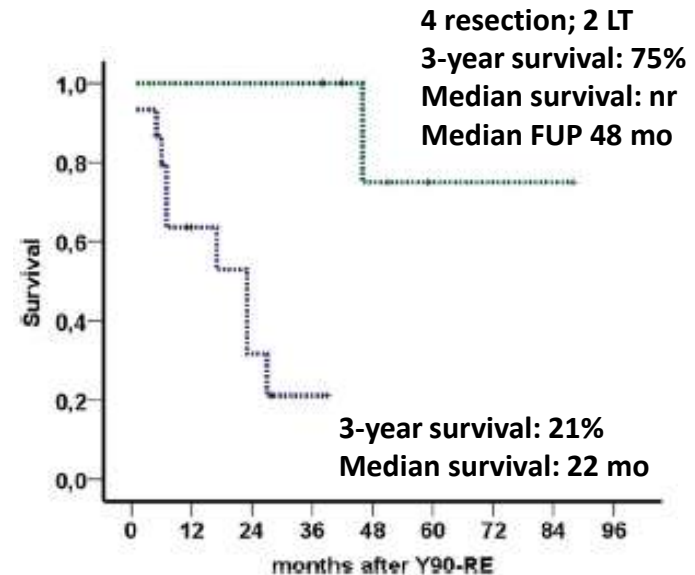


RE for HCC

Downstaging to Radical Therapy

- RE results in a higher rate of downsizing from UNOS T3 to T2 stage compared to TACE (58% vs. 31%, $p < 0.023$)¹.
 - Higher rate of RFA ablation (42% vs. 23%)
- Overall survival among UNOS T3 patients downstaged to resection or transplantation was achieved mainly in patients with single large tumors².

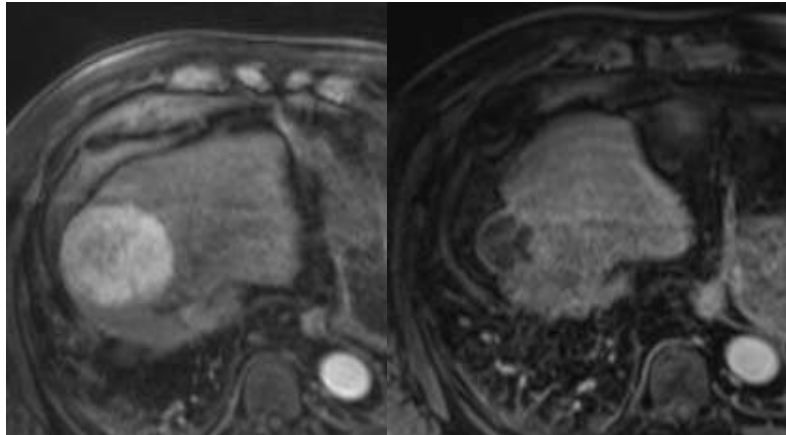
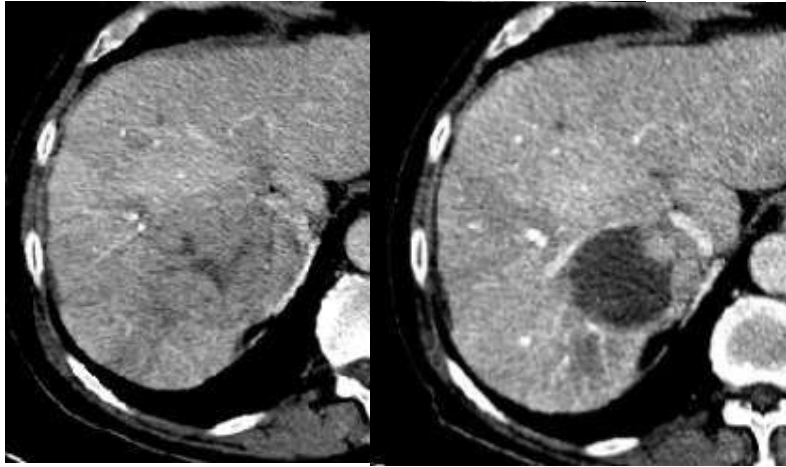
Pt	Cirrhosis	T Bili (mg/dL)	# nodules	Size (cm)
1	Yes	0.94	1	8.4
2	Yes	1.20	1	14.2
3	Yes	1.28	2	5.5
4	No	0.88	1	11.5
5	Yes	1.03	1	13.0
6	No	0.94	1	11.0



1. Lewandowski RJ, et al. Am J Transpl. 2009;9:1920–8.

2. Iñarrairaegui M, et al. Eur J Surg Oncol Eur J Surg Oncol. 2012;38:594–601 (and personal communication)

Complete Ablation after RE for HCC



35 patients submitted to LT after ^{90}Y -RE

Pre-treatment size 1–2.9 cm 3–5 cm > 5 cm

No. of nodules

9

17

12

Necrosis

100%

89%

65%

33%

> 50%

11%

12%

50%

< 50%

0%

23%

17%

Treatment of HCC in the Elderly Population

Retrospective analysis of 335 HCC patients treated at two U.S. tertiary institutions from 1998 to 2008 and divided into 2 groups:

- elderly (>70 years)
- younger (< 70 years)

Table 2. Treatments received

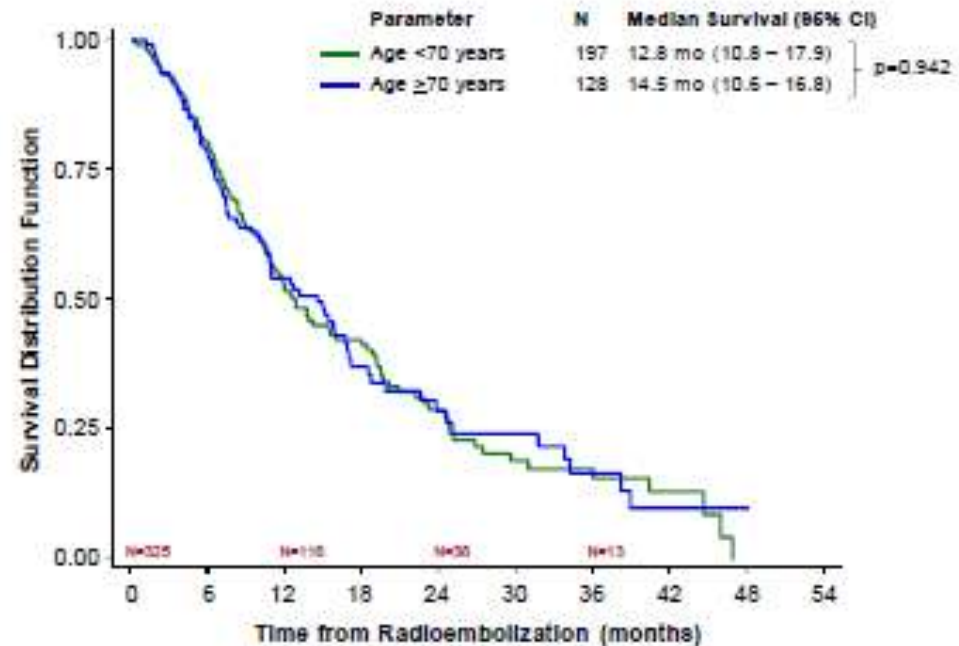
Patient characteristics	Younger (n = 240)	Elderly (n = 95)	Comparison (χ^2 test)
Transplantation	47 (19.6%)	5 (5.3%)	<i>p</i> = .0002
Observation	55 (22.9%)	35 (36.8%)	<i>p</i> = .0095
Surgery	41 (17.1%)	11 (11.6%)	<i>p</i> = .2098
Liver directed tx	87 (36.3%)	39 (41.1%)	<i>p</i> = .4134
Chemotherapy	86 (35.8%)	26 (27.4%)	<i>p</i> = .1388
Clinical trials	42 (18.2%)	15 (15.8%)	<i>p</i> = .6053 (missing = 9)

Treatment of HCC in the Elderly Population

Retrospective analysis of 325 HCC patients treated by radioembolization at 8 European centers (ENRY) and divided into 2 groups:

- elderly (>70 years)
- younger (< 70 years)

		≥ 70 y	< 70 y	p
Age (mean, range)		74.3 (70-87)	58.1 (22-69)	<0.001
Cirrhosis		81.3%	76.6%	0.33
Prior Tx		45.3	39.1	0.30
BCLC	A	16%	16%	0.66
	B	27%	26%	
	C	56%	56%	
Child A		85%	81%	



Treatment Guidelines for HCC

AASLD PRACTICE GUIDELINE

Management of Hepatocellular Carcinoma: An Update

Clinical Practice Guidelines

 **EASL** EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | **JOURNAL OF HEPATOLOGY**

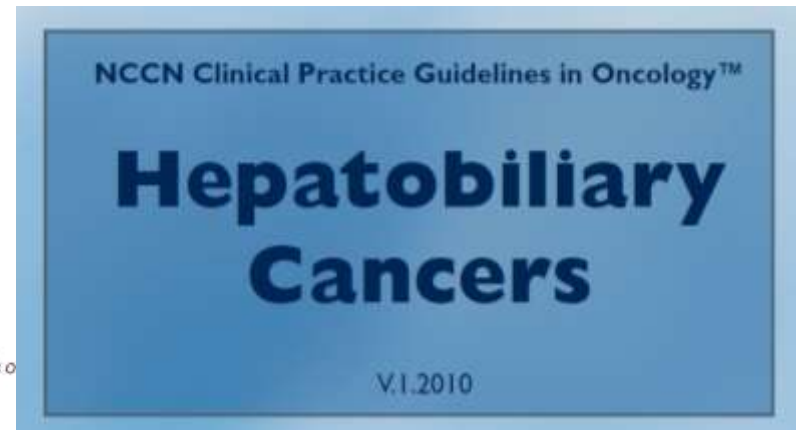
EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

GUIDELINES

Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma

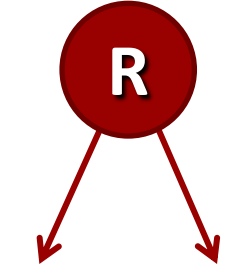
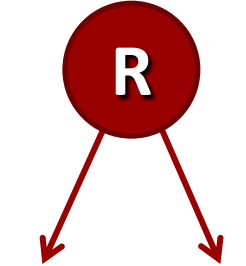
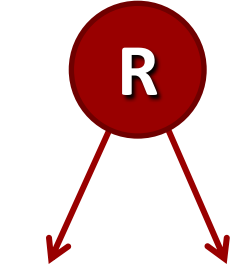
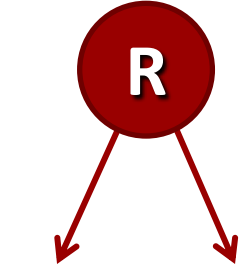
clinical practice guidelines

Annals of



Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Ongoing Clinical Trials in Intermediate and Advanced HCC

TRIAL	SIRveNIB ²	SARAH ³	SORAMIC ⁴	STOP ⁵
	N=360	N=400	N=665	N=400
Study Design				
Endpoint	OS	OS	OS	OS
Country	Asia-Pacific	France	Germany	Worldwide

1. <http://clinicaltrials.gov/ct2/show/NCT01135056>; 2. <http://clinicaltrials.gov/ct2/show/NCT001482442>; 3. <http://clinicaltrials.gov/ct2/show/NCT01126645>; 4. <http://clinicaltrials.gov/ct2/show/NCT01556490>.

SAFETY OF RE COMBINED WITH SORAFENIB

AN INTERIM ANALYSIS OF THE RCT SORAMIC



	RE + Sorafenib	Sorafenib
Median sorafenib dose	614 mg (45-793)	557mg (284-792)
Median duration	8.5 months	9.6 months

Adverse Event (%)	Sorafenib + RE (n=20)		Sorafenib only (n=20)		p-Value	
	All-Grade (%)	Grade 3/4/5 (%)	All Grade (%)	Grade 3/4/5 (%)	All-Grade	Grade 3/4/5
Elevated AST	90	0/0/0	90	15/0/0	1.000	0.231
Thrombocytopenia	90	0/0/0	65	0/0/0	0.127	-
Hypertension	73.7	21/0/0	89.5	26/0/0	0.405	1.000
Weight loss	70	5/0/0	68.4	5/0/0	1.000	1.000
Anemia	60	5/0/0	70	10/0/0	0.741	1.000
Diarrhea	55	20/0/0	55	20/0/0	1.000	1.000
Hypoalbuminemia	45	0/0/0	36.8	5/0/0	0.748	1.000
Hyperbilirubinemia	40	5/0/0	45	10/0/0	1.000	1.000
Fatigue	40	15/5/0	40	10/0/0	0.748	0.661
HFSR	35	20/0/0	35	15/0/0	1.000	1.000
Ascites	25	10/0/0	20	10/0/0	1.000	1.000
Nausea	15	5/0/0	10	0/0/0	1.000	1.000
Infection	10	5/0/0	50	20/0/0	0.014	0.342
Anorexia	5	0/0/0	30	10/0/0	0.092	0.487
Hemorrhage	5	0/0/5	15	5/0/5	0.605	1.000

Suggested Indications of RE for HCC

Conventional

(based on retrospective and prospective cohort studies and case-control studies)

Intermediate HCC

- Single, multinodular (2-3 or tumor burden < 20% of the liver parenchyma) Child-Pugh A, normal liver function, PS 0
- Multifocal (bilobar or tumor burden 20%– 40% of the liver parenchyma), PS 0, *only if* bilirubin < 2mg/dL

Advanced HCC:

- No extra-hepatic disease, branch or main portal vein invasion, with normal liver function, PS 0

Suggested Indications of RE for HCC

Investigational

(based on case-reports or single center uncontrolled studies)

- Radiation-induced segmentectomy, for patients unfit for ablation or embolization
- Radiation induced lobectomy associated to tumor treatment, for patients unfit for surgery due to co-morbidities, or insufficient remnant liver
- Down-staging procedure before resection or transplantation in case of intermediate-advanced HCC (exceeding conventional criteria)

Maraming salamat

Thank you