Integrating Systemic and Loco-Regional Therapies in Patients with Advanced HCC

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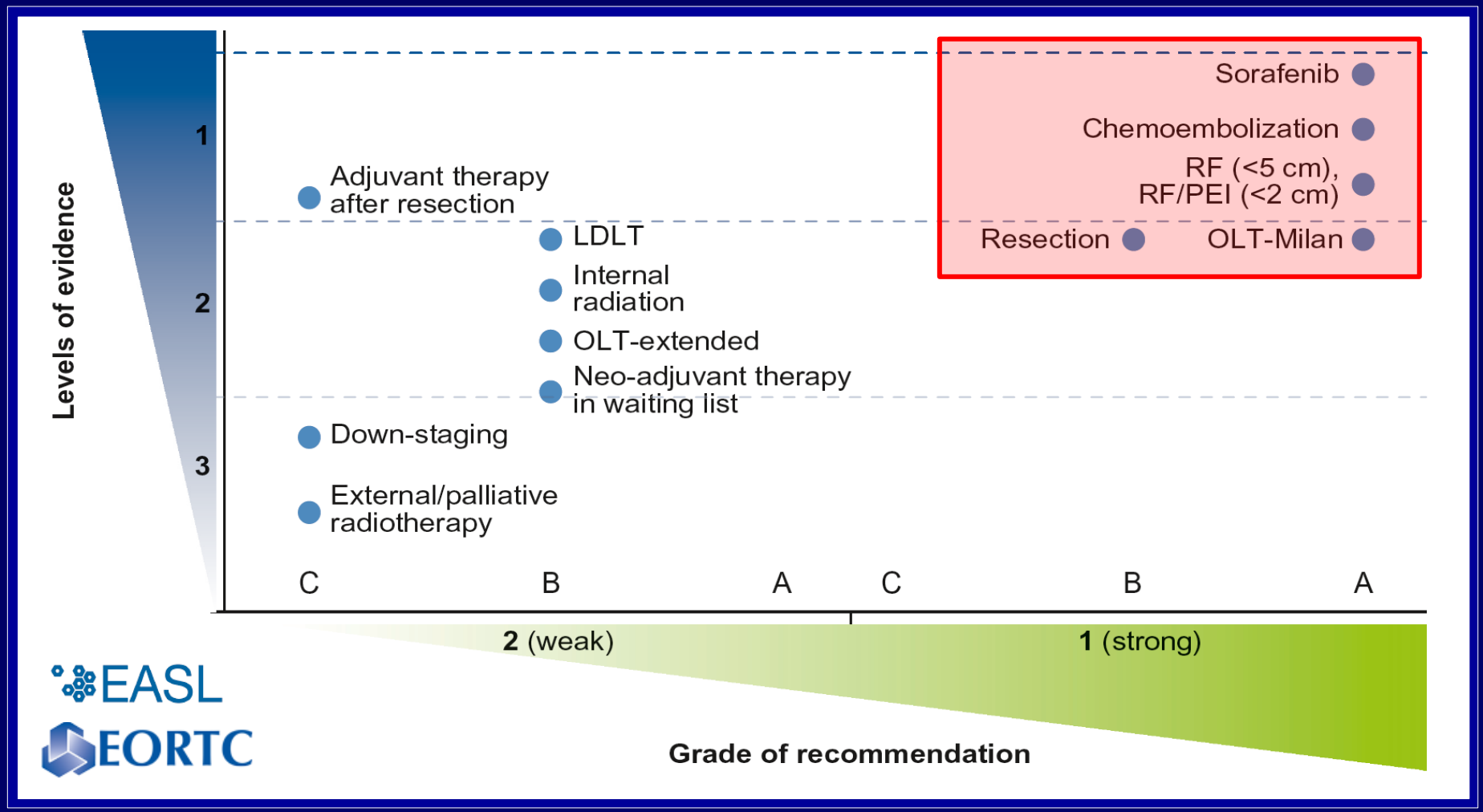
EASL-EORTC Clinical Practice Guidelines: Levels of Evidence vs Grade of Recommendation



Llovet JM, Ducreux M, Lencioni R et al. J Hepatol 2012;56:908-943 - Eur J Cancer 2012;48:599-641

ESMO-ESDO Clinical Practice Guidelines: BCLC Staging System and Treatment Strategy

clinical practice guidelines

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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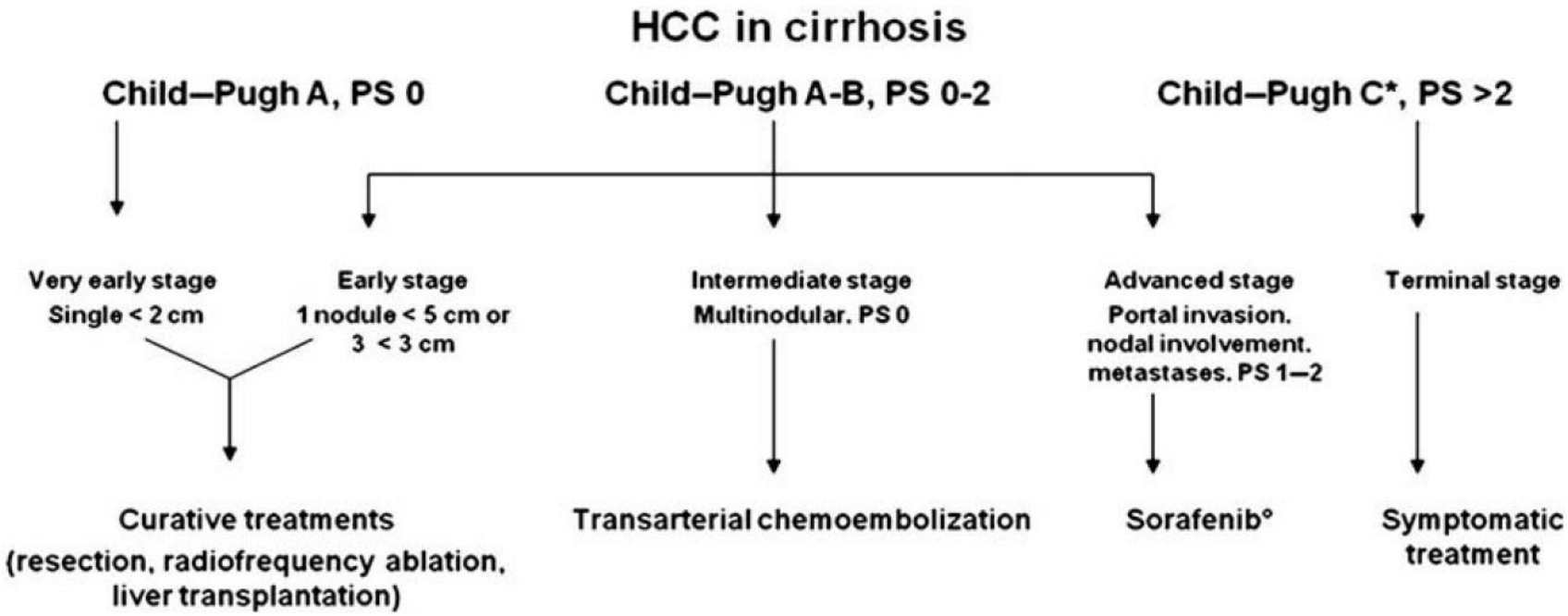
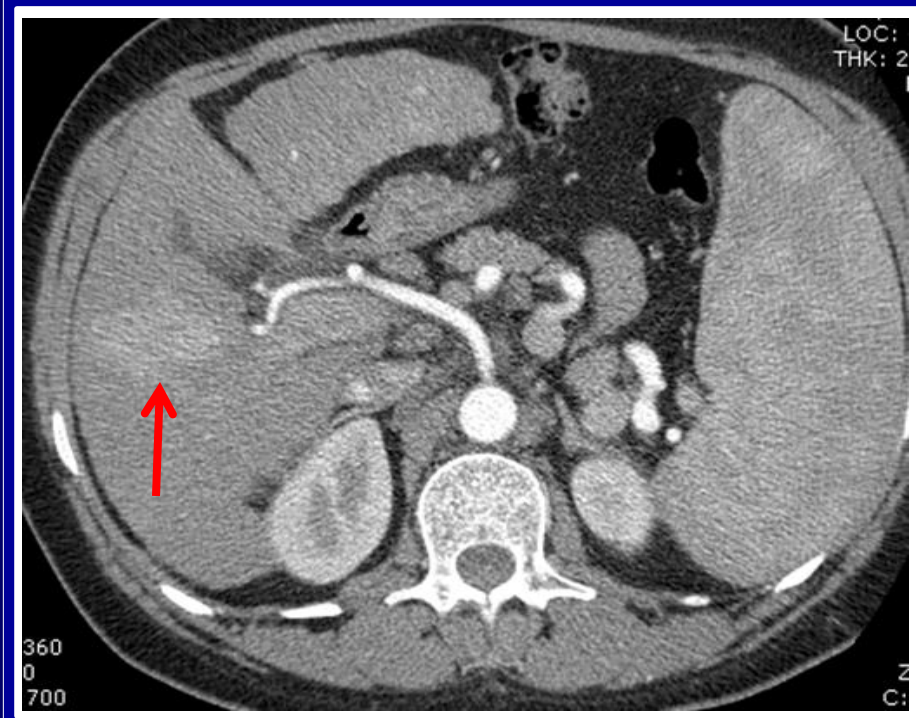


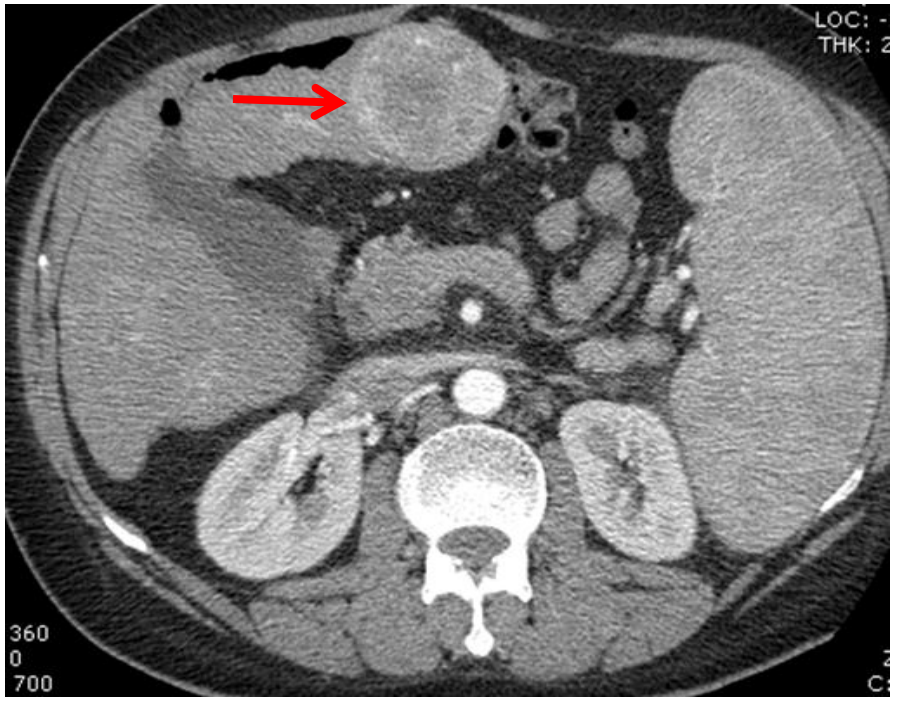
Verslype C et al. Ann Oncol 2012;23 Suppl 7:vii41-48

CASE #1:
Baseline Characteristics

- Male, 59 years old
- ECOG PS 0
- Hepatitis C related cirrhosis
- Child-Pugh class A
- Portal hypertension, splenomegaly, no ascites
- No major co-morbidity
- Large, multinodular HCC
- No evidence of portal vein invasion
- No evidence of extrahepatic spread

CASE #1:
Pre-Treatment CT Scans (Arterial-Phase)





CASE #1:
Treatment Options

- Liver Transplantation
- Surgical resection
- Local ablation
- Transarterial Chemoembolization (TACE)
- Transarterial Radioembolization (Y90)
- Sorafenib
- TACE + Sorafenib
- Y90 + Sorafenib
- Best supportive care

ESMO-ESDO Clinical Practice Guidelines: BCLC Staging System and Treatment Strategy

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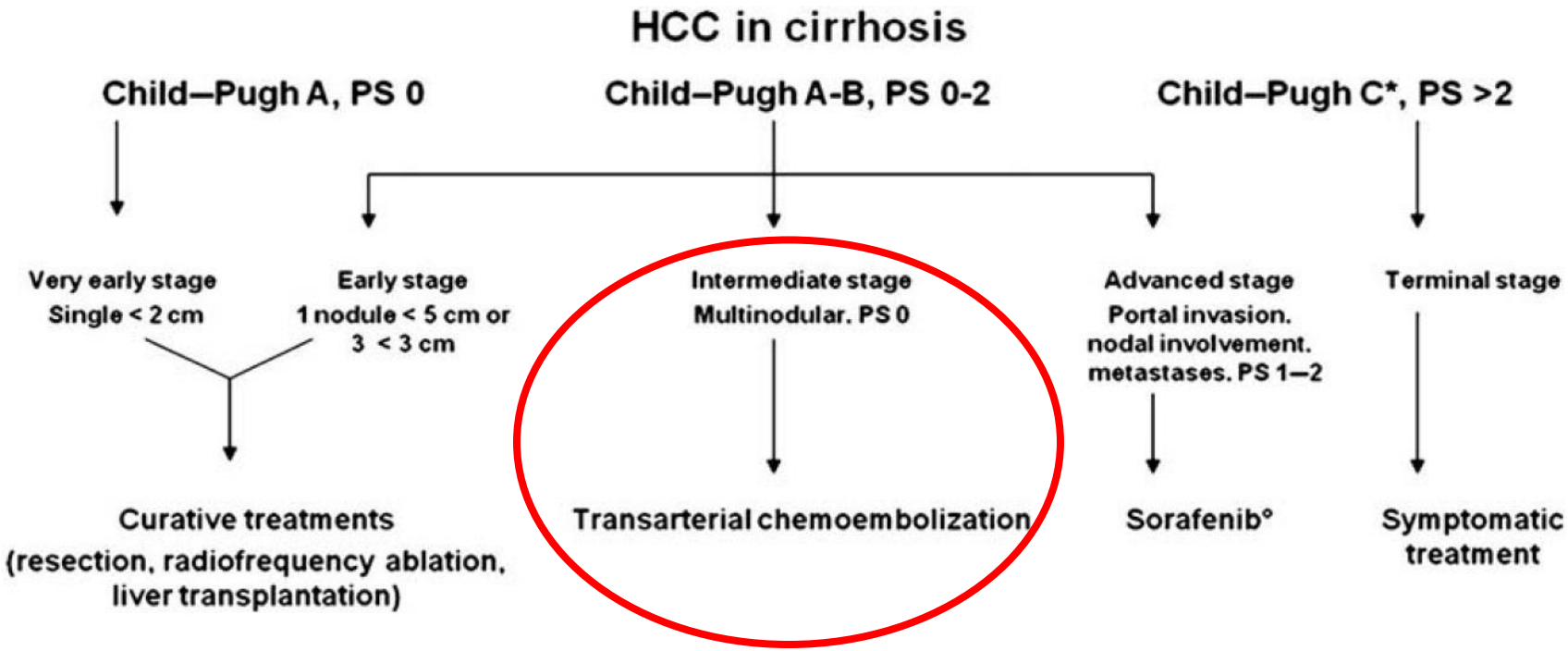
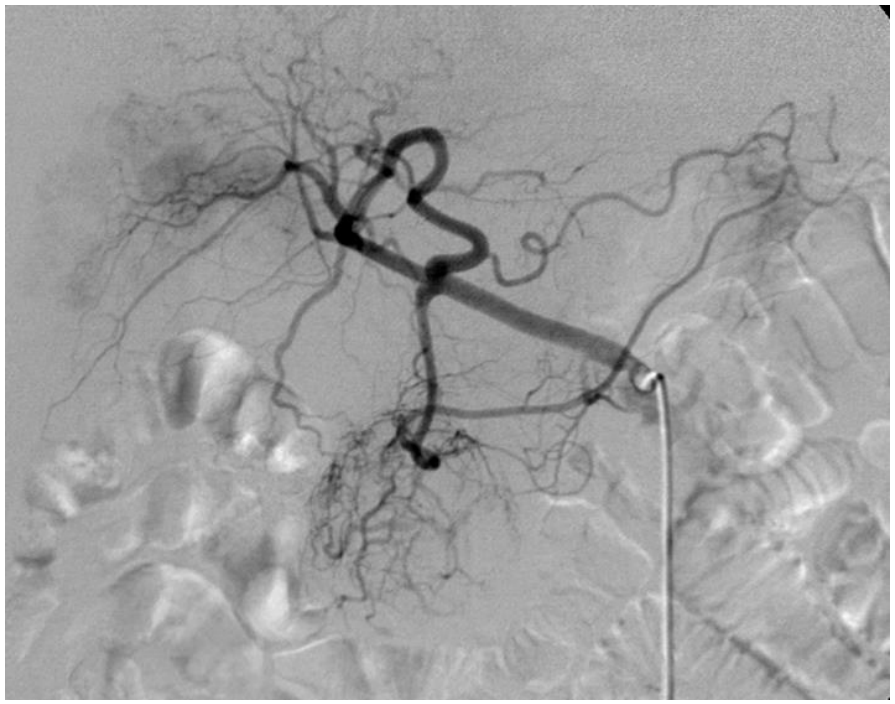
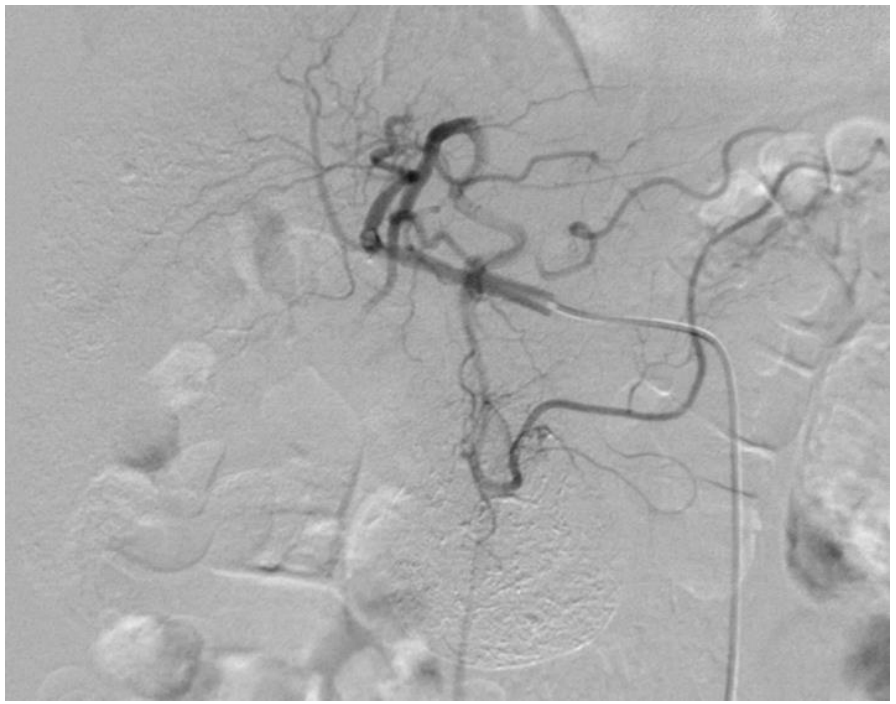


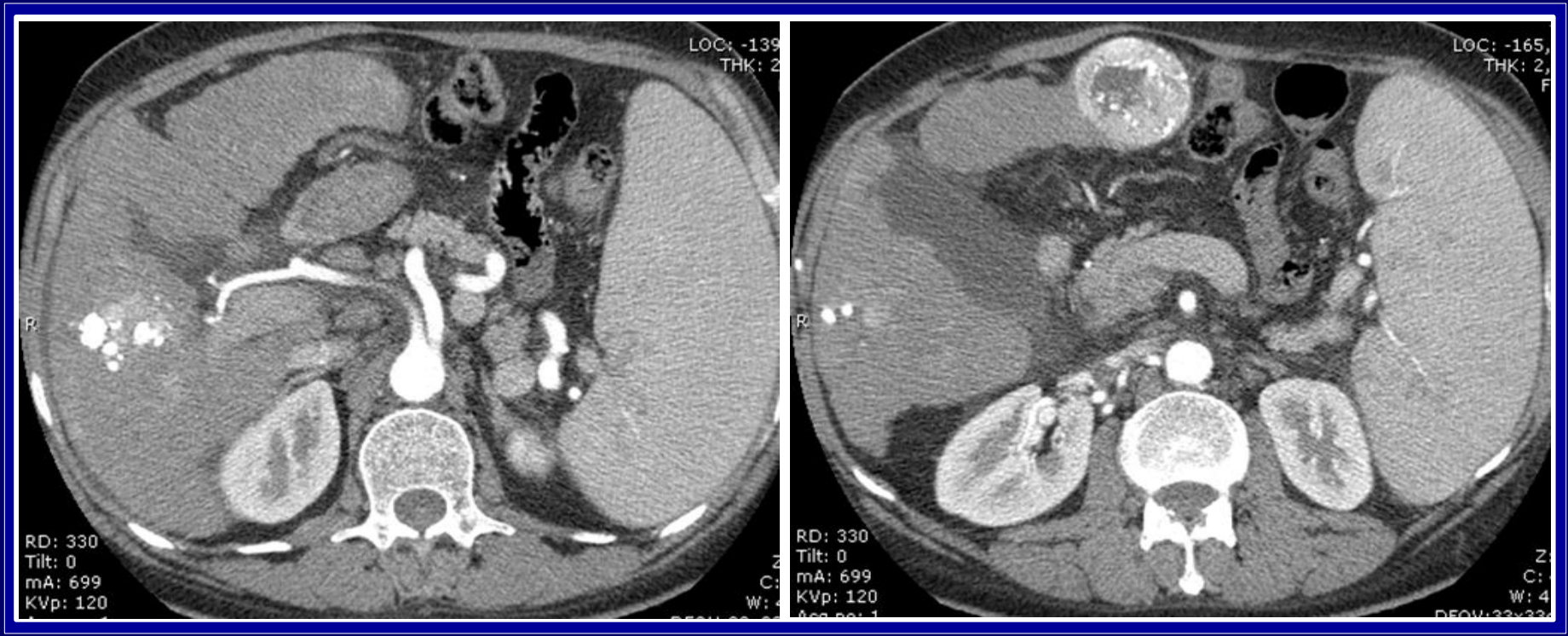
Verslype C et al. Ann Oncol 2012;23 Suppl 7:vii41-48

CASE #1:
TACE (Lipiodol, Doxorubicin, Gelfoam)





CASE #1:
Post-Treatment CT Scans (Arterial-Phase)



ESMO-ESDO Clinical Practice Guidelines: Response Assessment

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

- **Response assessment should be based on dynamic CT or MRI studies and the modified RECIST criteria (mRECIST)**

Verslype C et al. Ann Oncol 2012;23(Suppl. 7):41-48

Modified RECIST (mRECIST) for HCC: Overall Response Assessment

Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

Riccardo Lencioni, M.D.,[1] and Josep M. Llovet, M.D.[2,3]

Table 3 Overall Response Assessment in mRECIST: Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Lencioni R, Llovet JM. Semin Liver Dis 2010;30:52-60

Modified RECIST (mRECIST) for HCC: Non-Target Lesions / New Lesions

Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

Riccardo Lencioni, M.D.,[1] and Josep M. Llovet, M.D.[2,3]

mRECIST recommendations

Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.

RECIST, Response Evaluation Criteria In Solid Tumors; mRECIST, modified Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

Lencioni R, Llovet JM. Semin Liver Dis 2010;30:52-60

Modified RECIST (mRECIST) for HCC: Target Lesions Assessment

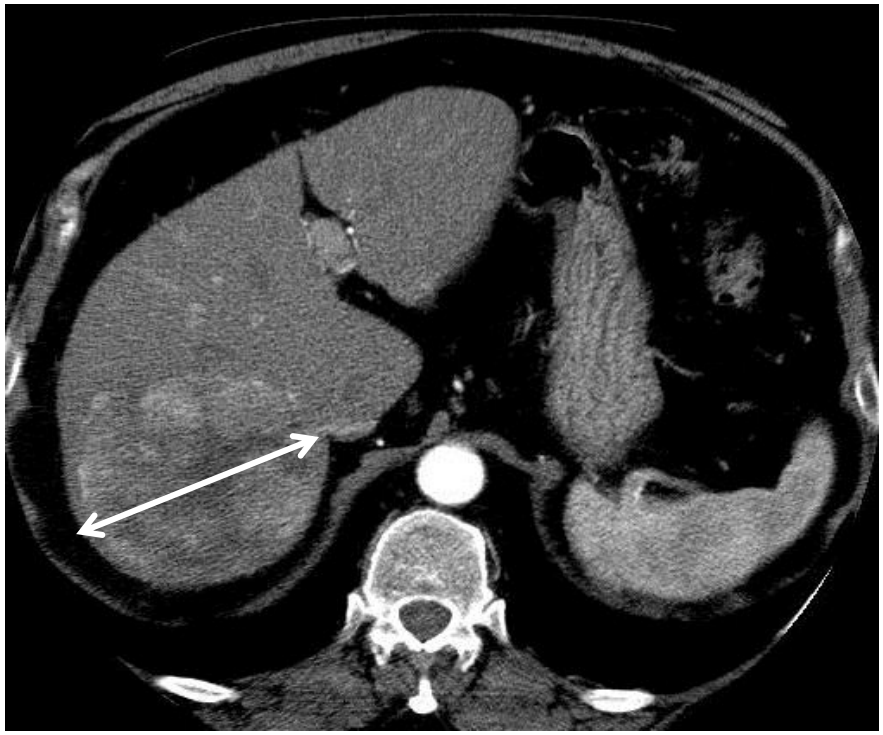
Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

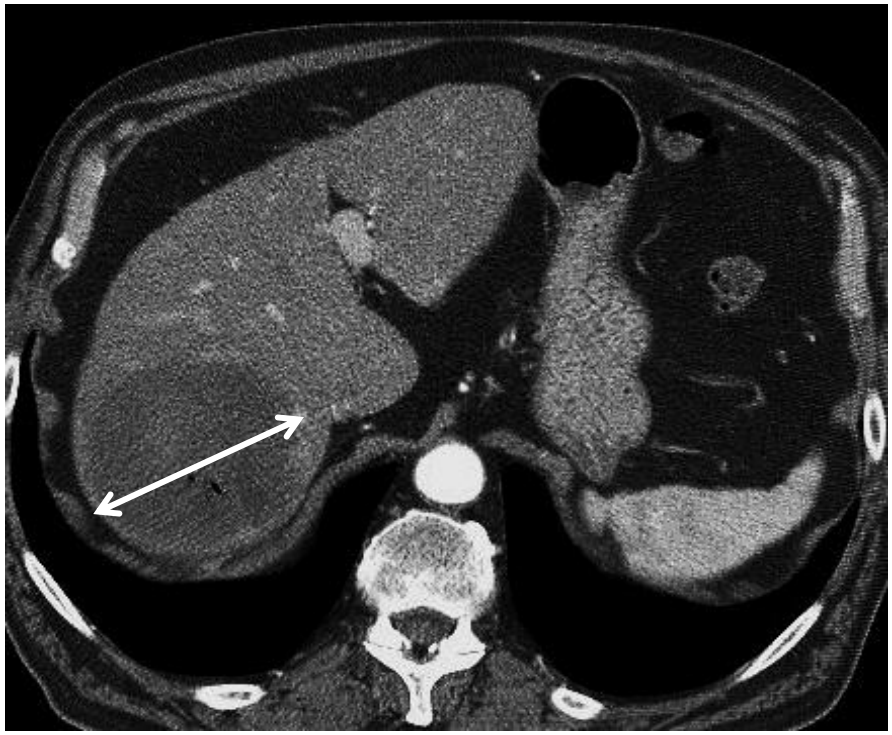
Riccardo Lencioni, M.D.,[1] and Josep M. Llovet, M.D.[2,3]

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

Lencioni R, Llovet JM. Semin Liver Dis 2010;30:52-60

Target Lesion Response after DEB-TACE: Standard RECIST vs mRECIST



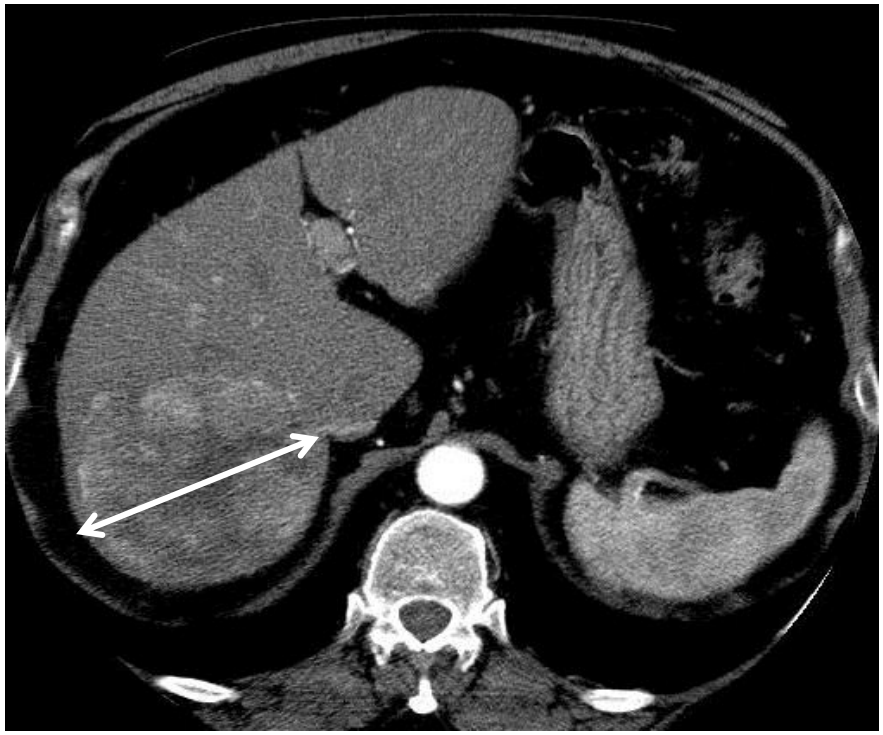


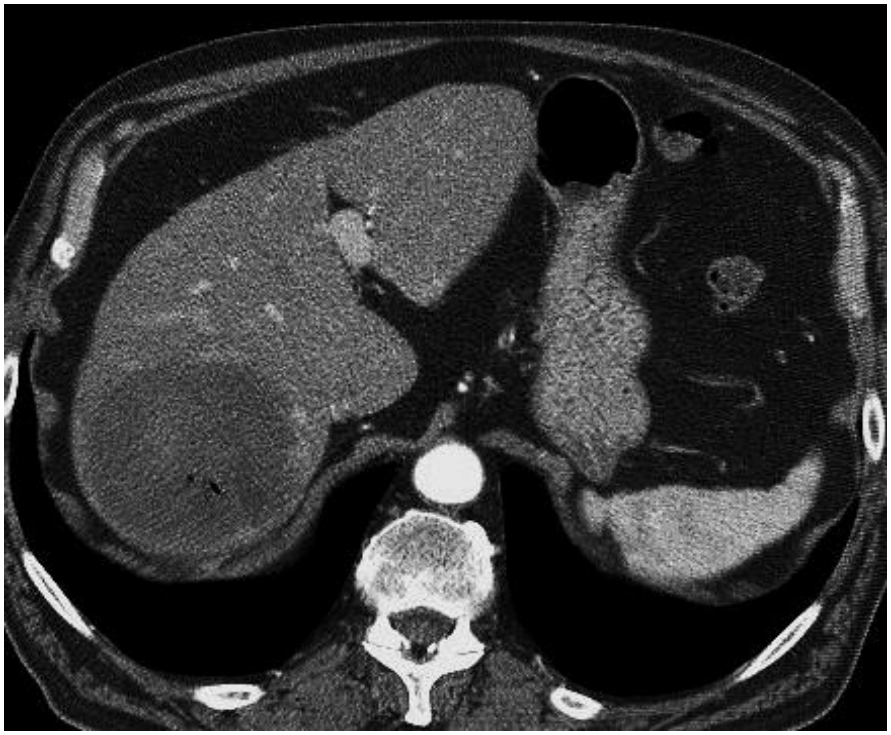
Baseline Arterial-Phase CT Scan ***Post-Baseline Arterial-Phase CT Scan***

Standard RECIST: Stable Disease

Lencioni R et al. Semin Intervent Radiol 2013;30:3–11

Target Lesion Response after DEB-TACE: Standard RECIST vs mRECIST





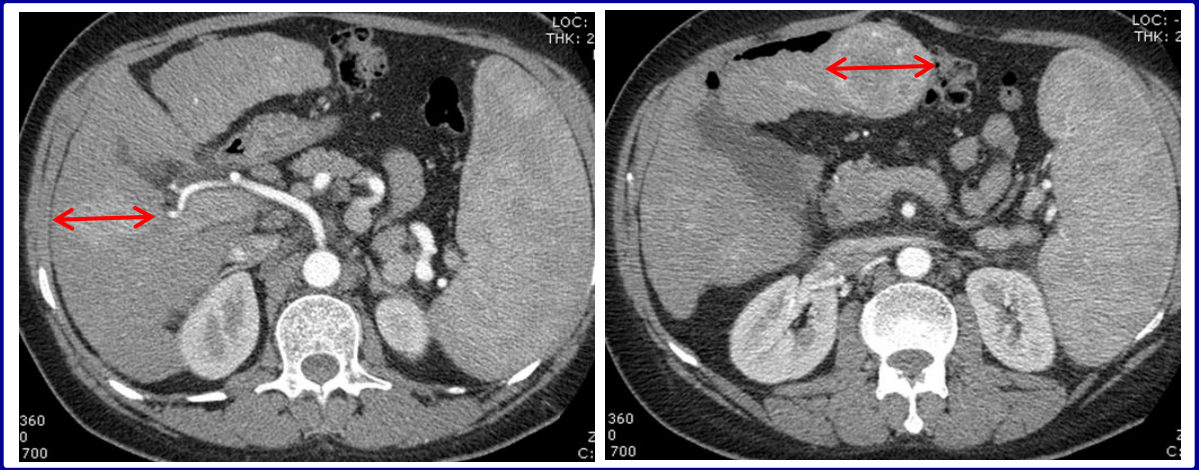
Baseline Arterial-Phase CT Scan ***Post-Baseline Arterial-Phase CT Scan***

mRECIST: Complete Response

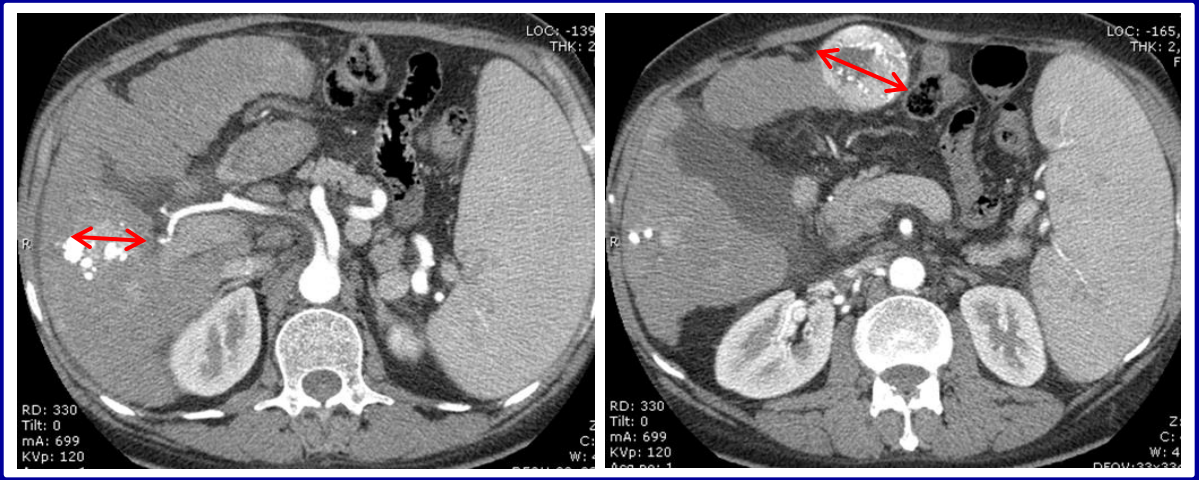
Lencioni R et al. Semin Intervent Radiol 2013;30:3–11

CASE #1:
Target Lesions Response Assessment (mRECIST)

Baseline



1-month post TACE

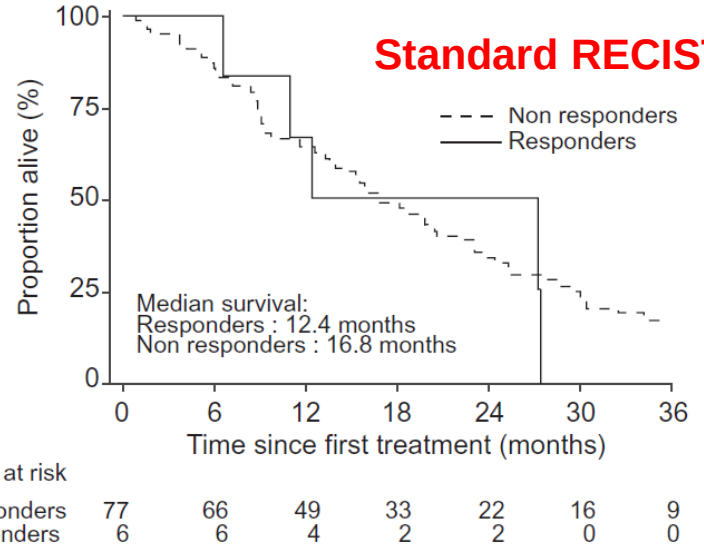


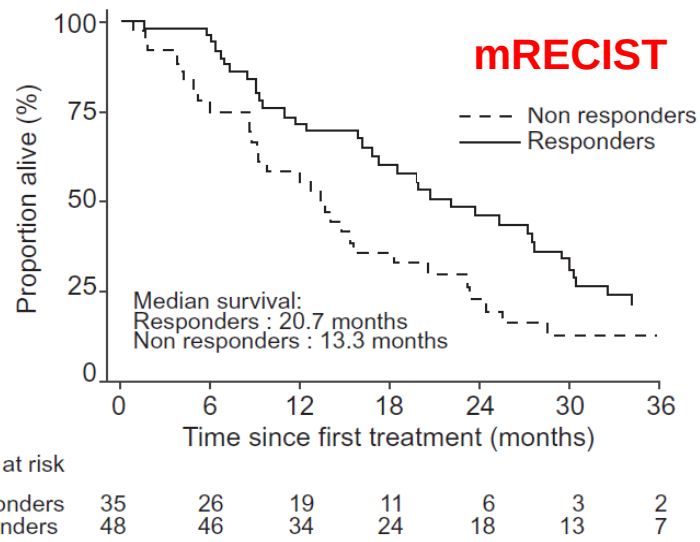
SD

Survival Outcomes after TACE According to mRECIST Response

	Number of patients (%)		
	RECIST 1.1	EASL	mRECIST
CR	0	17 (20%)	17 (20%)
PR	6 (7%)	32 (38%)	31 (37%)
SD	54 (65%)	12 (14%)	13 (16%)
PD	23 (28%)	22 (27%)	22 (27%)

Overall response	OS (95% CI)	*p* value
EASL*		
Non-responder (n = 33)	1.00	0.027
Responder (n = 45)	0.56 (0.34-0.94)	
mRECIST*		
Non-responder (n = 34)	1.00	0.037
Responder (n = 44)	0.58 (0.35-0.97)	

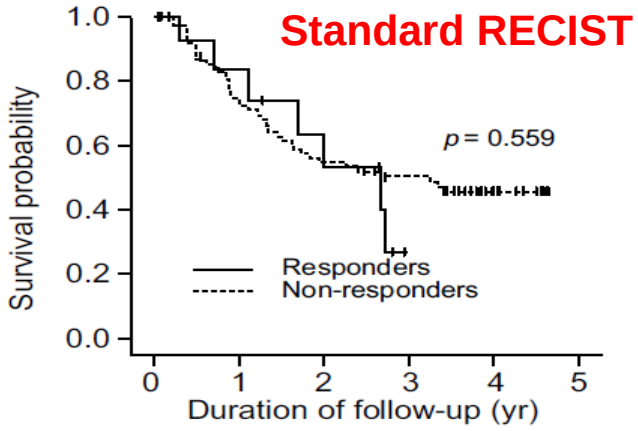




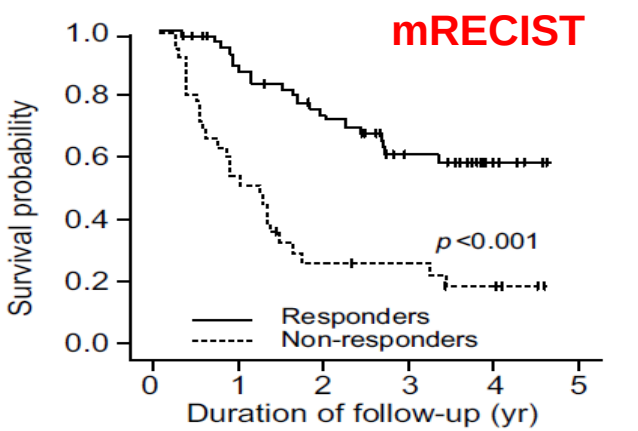
Gillmore R et al. J Hepatol 2011;55:1309-1316

Survival Outcomes after TACE According to mRECIST Response

Variables	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
WHO responder	0.89 (0.38-2.10)	0.795	-	-
RECIST responder	1.27 (0.57-2.85)	0.559	-	-
EASL responder	0.21 (0.12-0.37)	<0.0001	0.21 (0.11-0.40)	<0.0001
mRECIST responder	0.27 (0.15-0.48)	<0.0001	0.31 (0.17-0.59)	<0.0001



Number at risk						
Responders	13	1	0	0	0	0
Non-responders	85	73	61	49	37	25

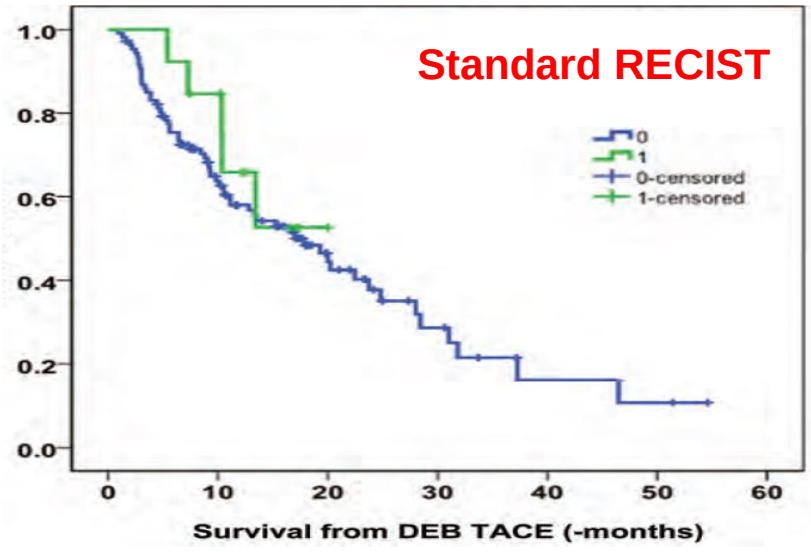


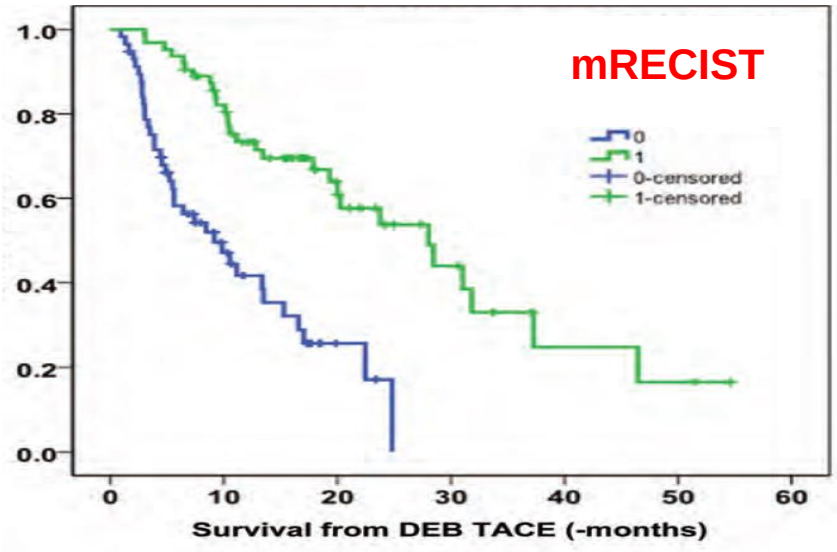
Number at risk						
Responders	62	48	36	24	12	0
Non-responders	36	23	11	0	0	0

Jung ES et al. J Hepatol 2013;58:1181-1187

Survival Outcomes after TACE According to mRECIST Response

WHO					
Responders	5	10.4 (10.2–10.4)	0.72	1	0.22
Non-responders	115	17.8 (11.8–23.8)		0.32 (0.05–1.96)	
RECIST1.1					
Responders	13	15.2 (12.0–18.4)	0.5	1	0.92
Non-responders	107	17.8 (11.4–24.2)		0.93 (0.21–4.06)	
mRECIST					
Responders	63	28.0 (18.0–38.0)	<0.0001	1	0.013
Non-responders	57	9.1 (04.4–13.9)		2.5 (1.22–5.13)	
EASL					
Responders	47	28.4 (19.7–37.1)	<0.0001	1	0.064
Non-responders	73	10.5 (06.6–14.3)		2.07 (0.95–4.5)	





Prajapati HJ et al. Ann Oncol 2013;24:965-973

Concept of Treatment Stage Migration in the Therapeutic Management of HCC

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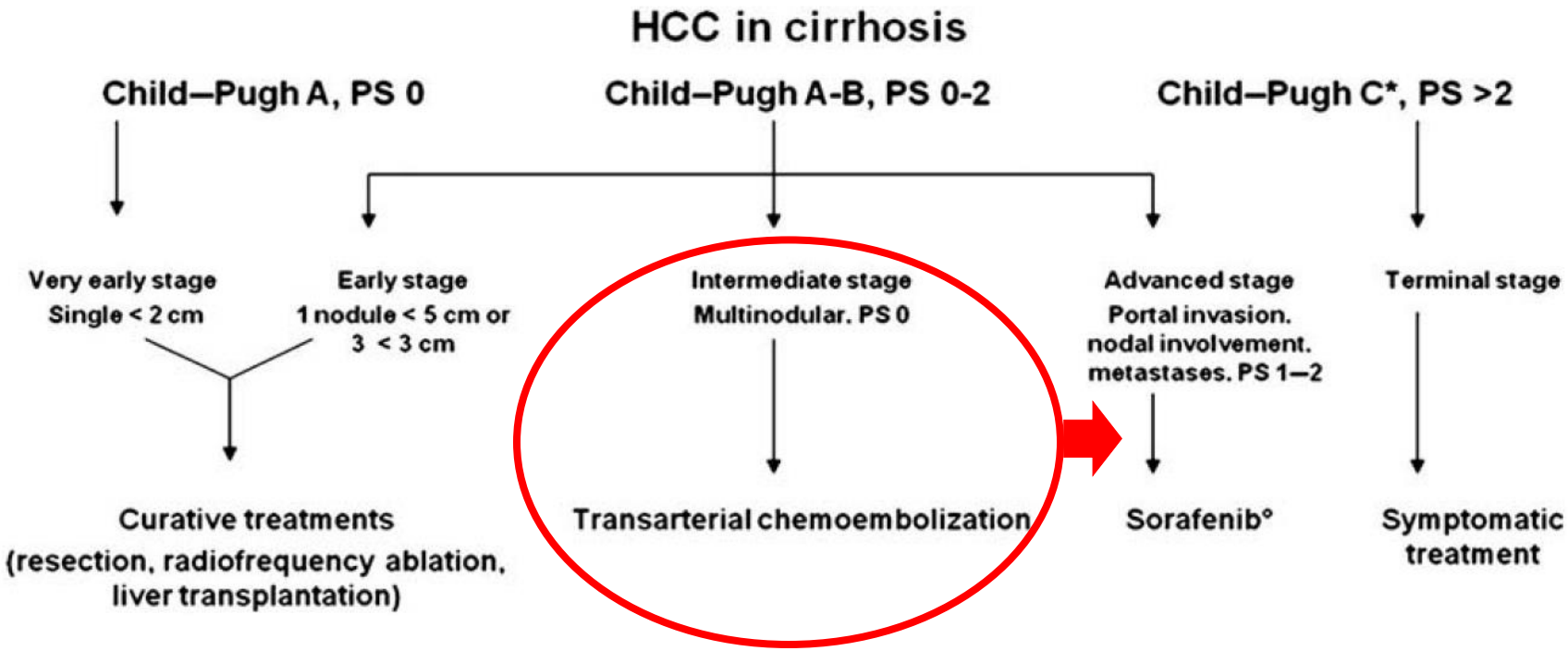


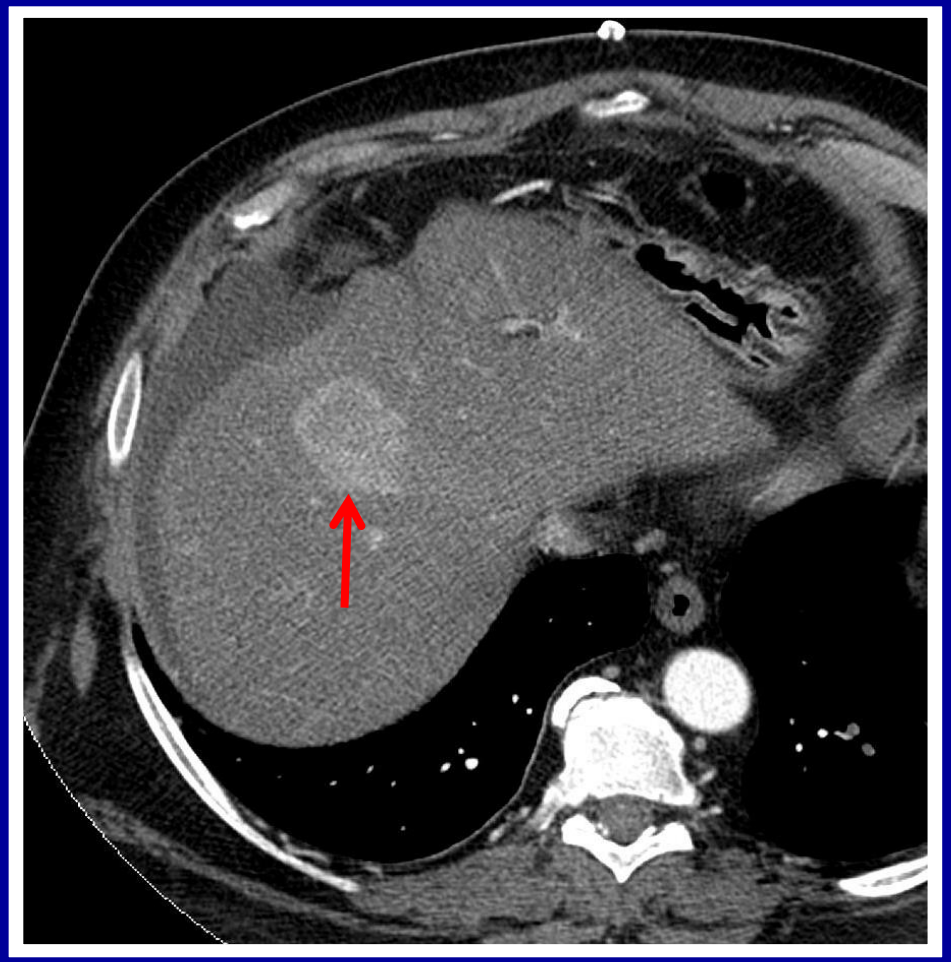
Verslype C et al. Ann Oncol 2012;23 Suppl 7:vii41-48

CASE #2:
Baseline Characteristics

- Female, 73 years old
- ECOG PS 1
- Hepatitis C related cirrhosis
- Child-Pugh class A
- No evidence of portal hypertension, no ascites
- No major co-morbidity
- Single HCC 4 cm
- No evidence of portal vein invasion
- No evidence of extrahepatic spread

CASE #2:
Treatment Options

- Liver Transplantation
- Surgical resection
- Local ablation
- TACE
- Y90
- Sorafenib
- TACE + Sorafenib
- Y90 + Sorafenib
- Best supportive care



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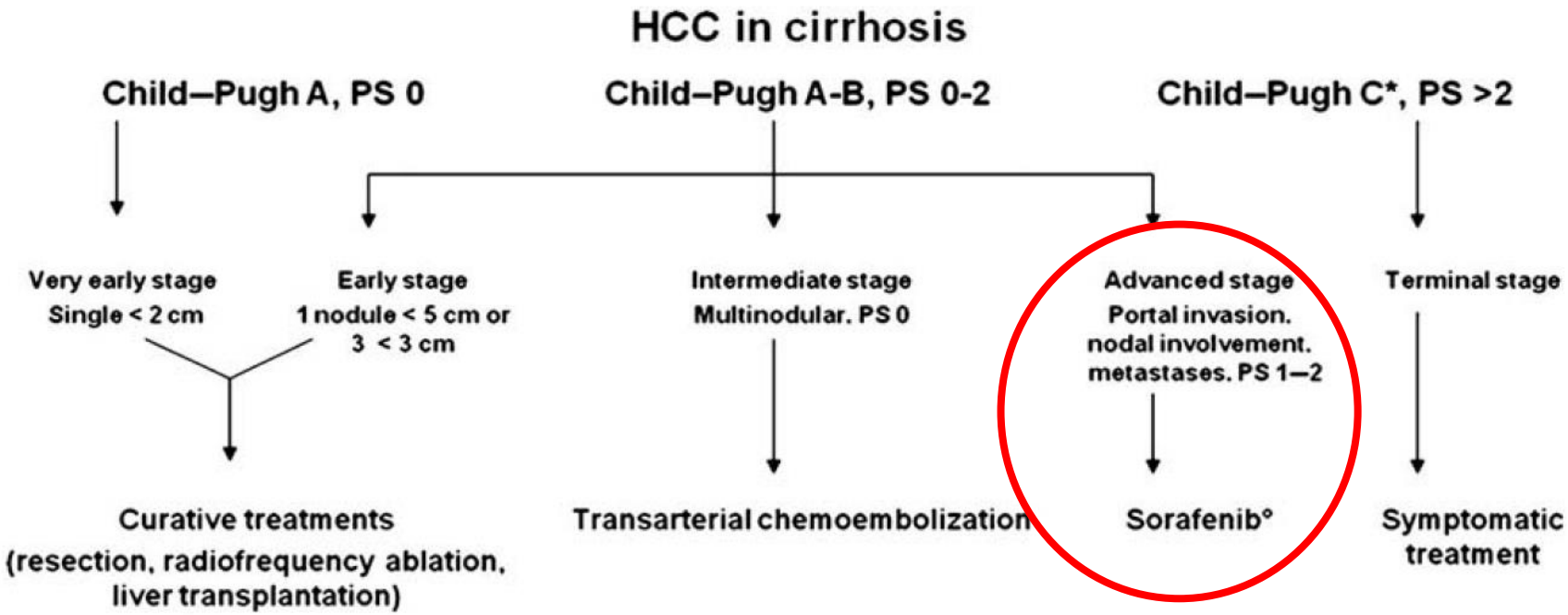
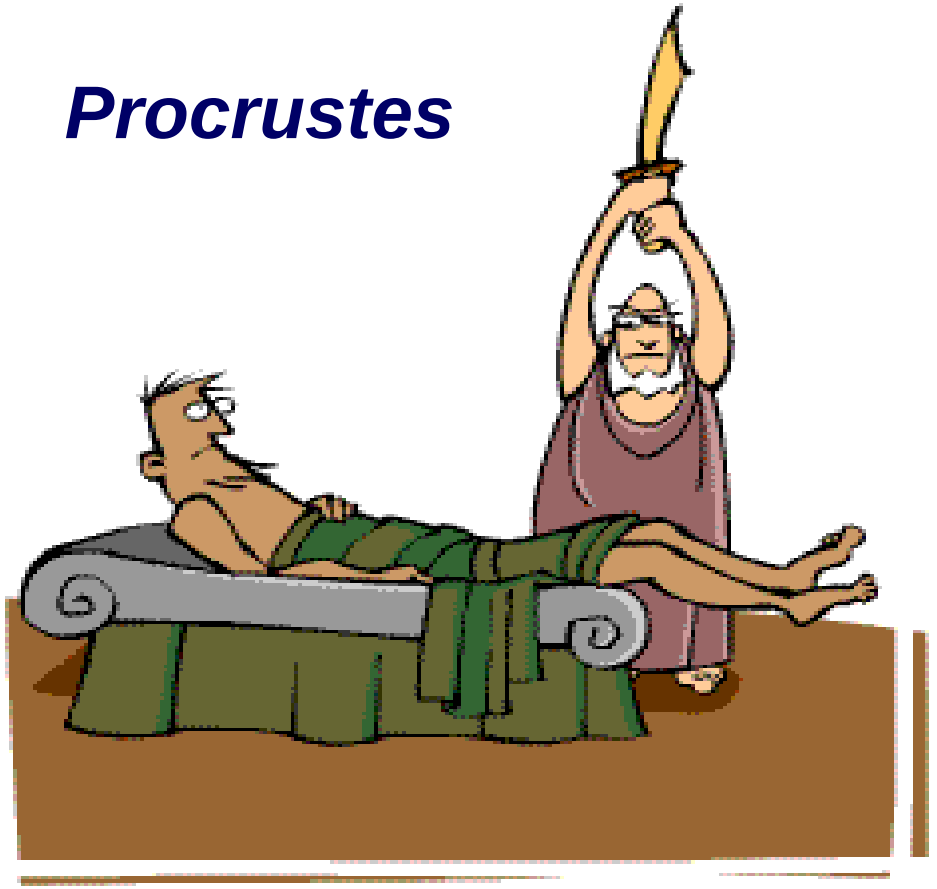


Verslype C et al. Ann Oncol 2012;23 Suppl 7:vii41-48

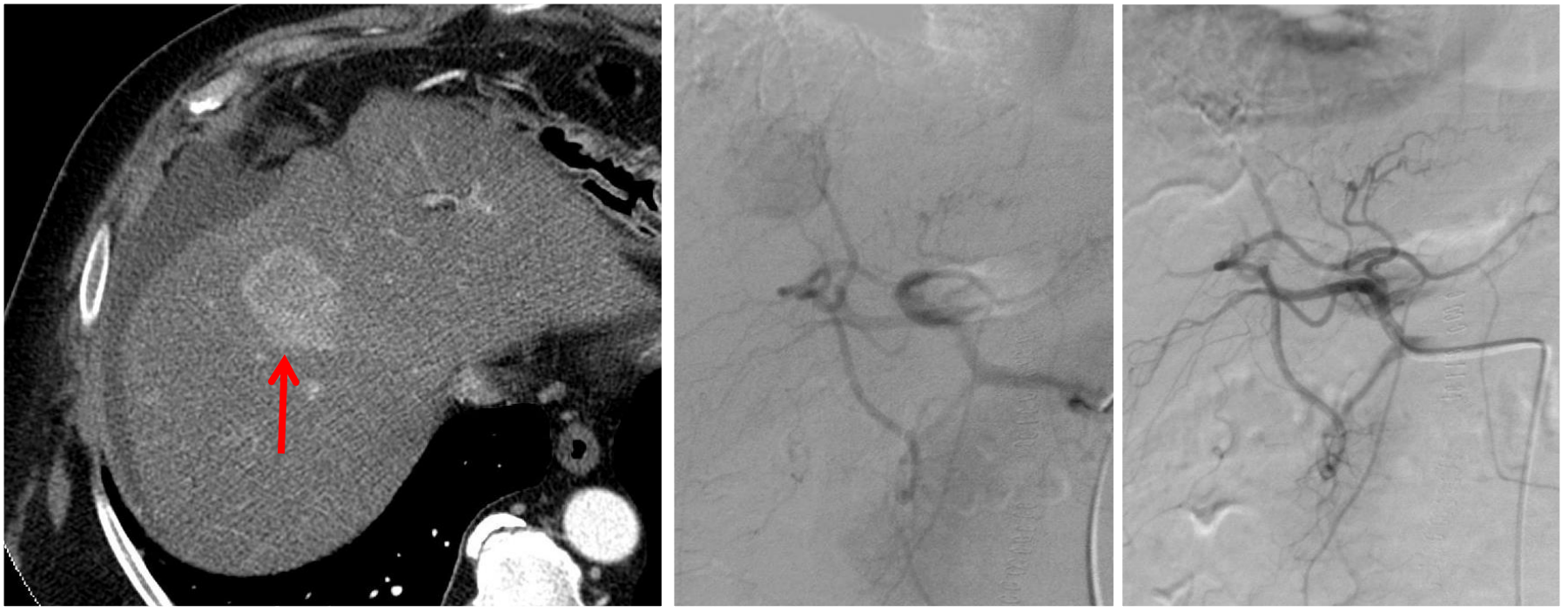
HCC on the Procrustean Bed of Staging Systems and Treatment Allocation Strategies

Procrustes

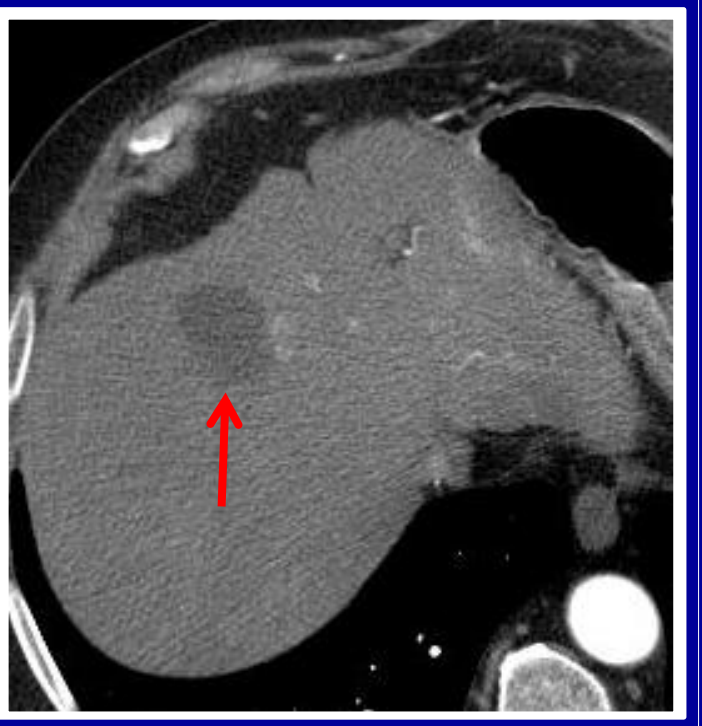


Mazzaferro V, Lencioni R, Majno P. Semin Liver Dis 2015 (in press)

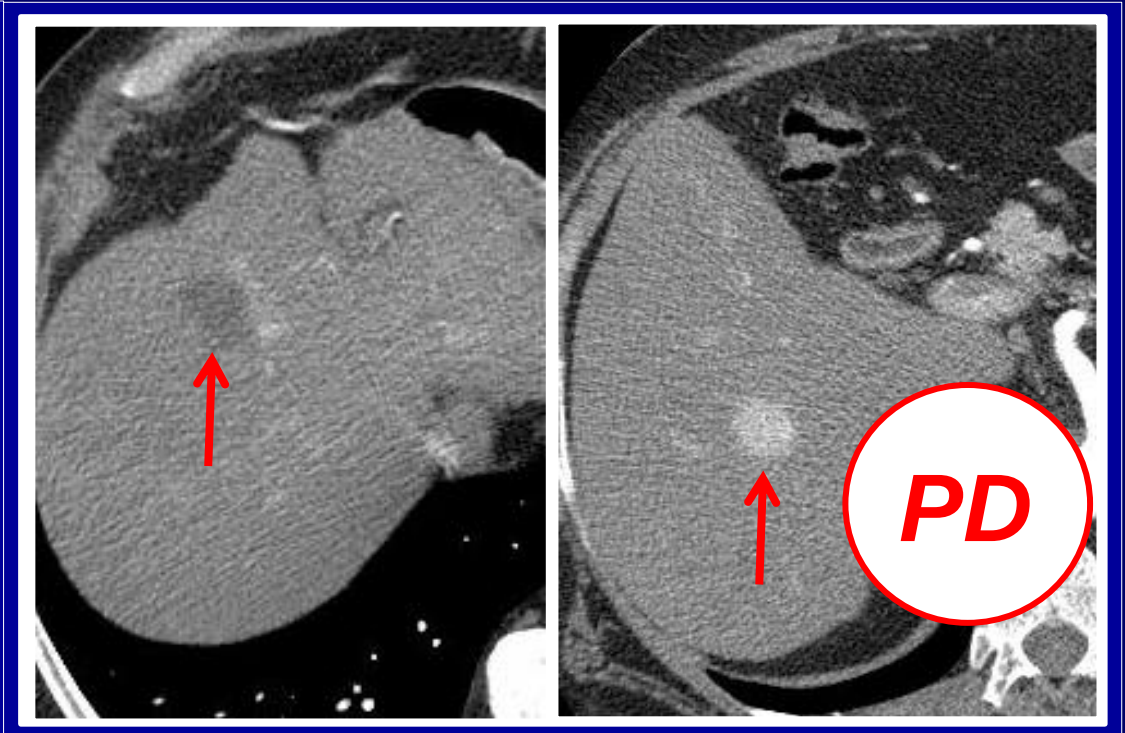
CASE #2:
Pre-Treatment CT Scans and Segmental TACE



CASE #2:
Follow-up CT Scans after TACE

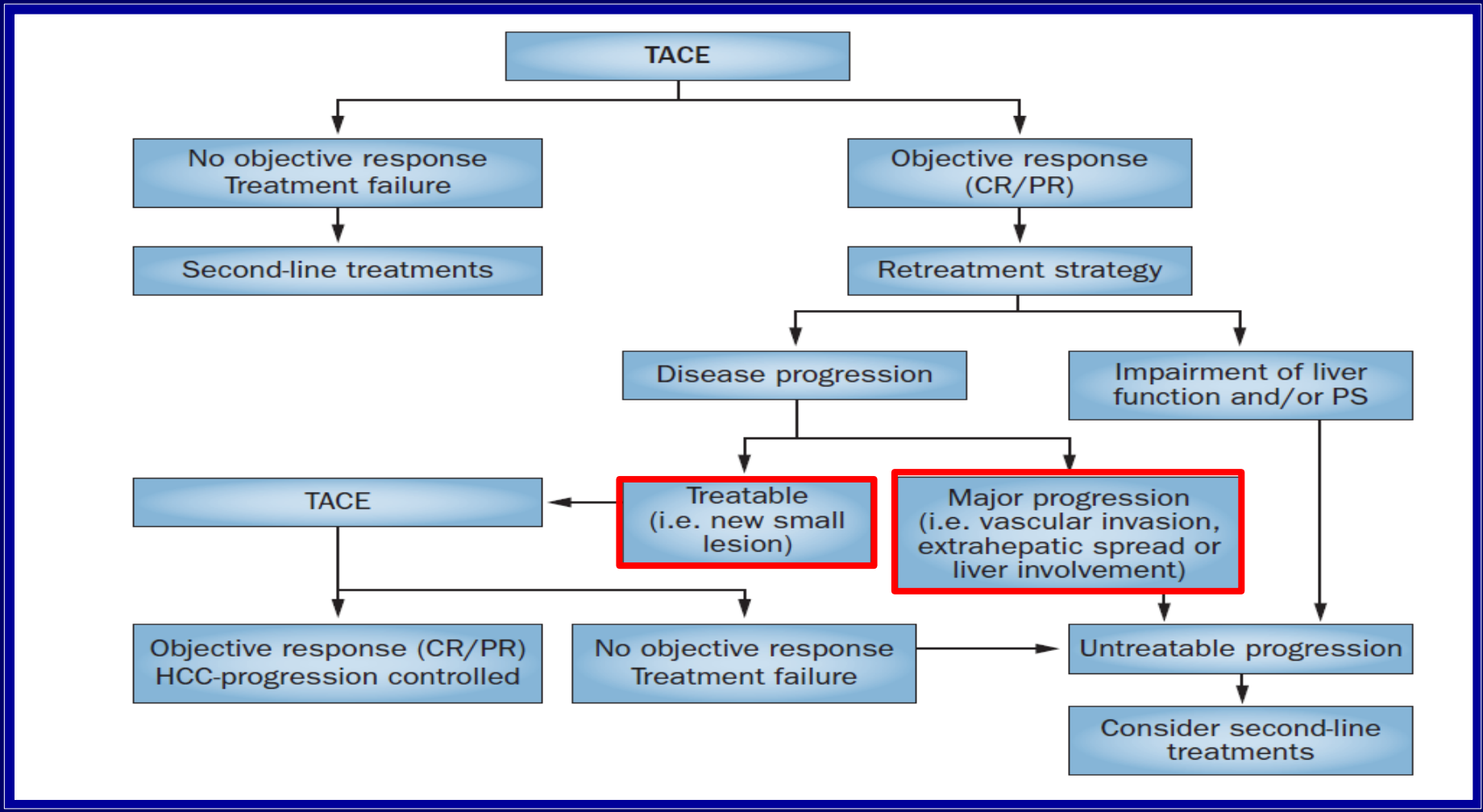


1-month



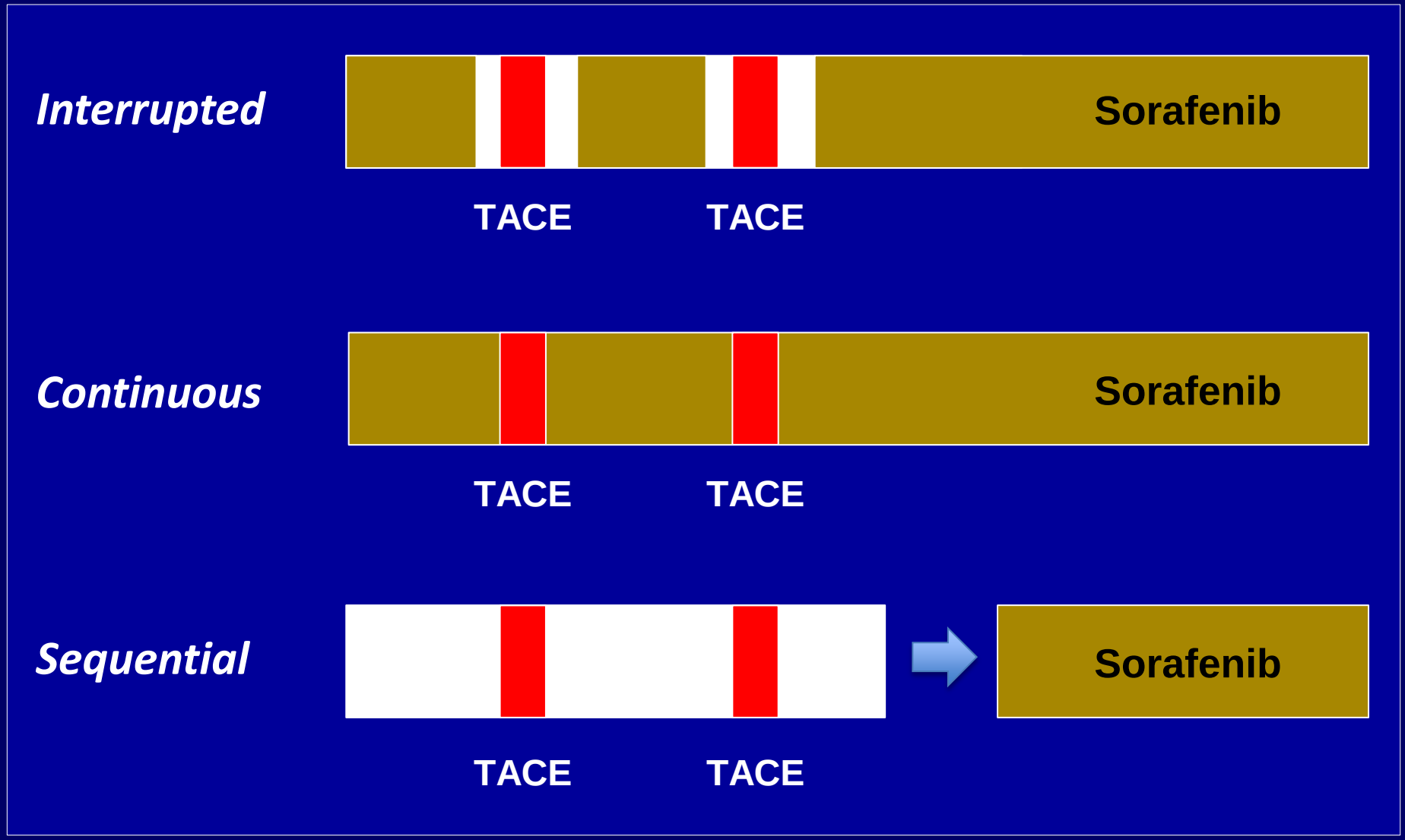
3-month

Proposed Treatment Algorithm after First-Line TACE Therapy

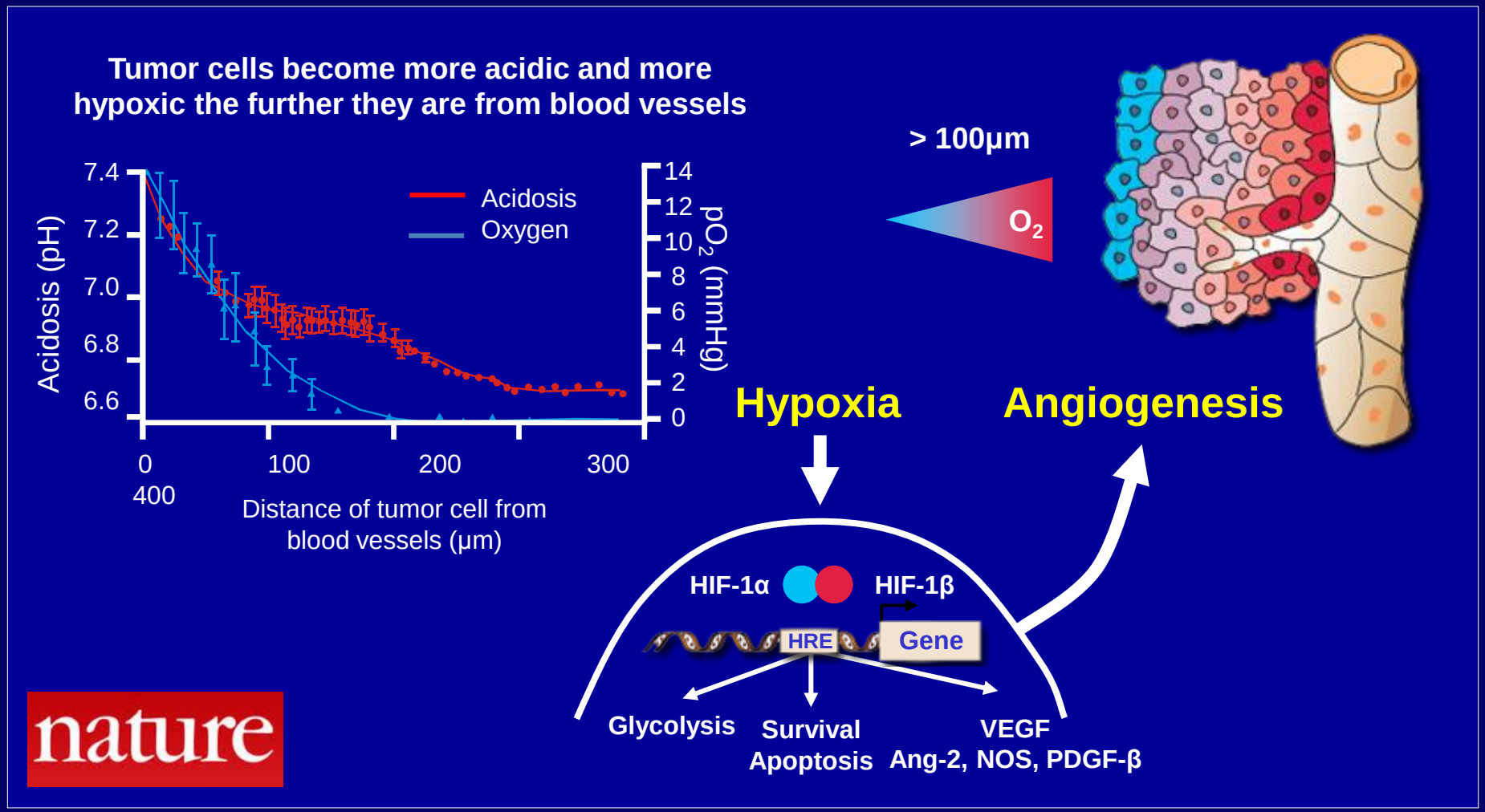


Forner A et al. Nat Rev Clin Oncol 2014;11:525–535

Integrating Systemic and Loco-Regional Therapies in Patients with Advanced HCC



Hypoxia in the post-TACE Micro-Environment Leads to Angiogenesis



Carmeliet P, Jain RK. Nature 2000;407(6801):249-257

SPACE Clinical Trial: Sorafenib or Placebo in Combination with DEB-TACE

A Phase II Randomized, Double-blind, Placebo-controlled Study of Sorafenib or Placebo Combined with DEB-TACE for the Treatment of Intermediate HCC (the SPACE Study)

www.clinicaltrials.gov - NCT00692770

Inclusion Criteria

- Unresectable HCC
- Multinodular HCC
- Child–Pugh A without ascites or encephalopathy
- ECOG PS 0

Exclusion Criteria

- EHS / VI
- TACE contraindications

Randomization 1:1

Stratification

- Serum AFP
- Geographical region

n = 304

DEB-TACE + sorafenib

DEB-TACE + placebo

Primary Endpoint

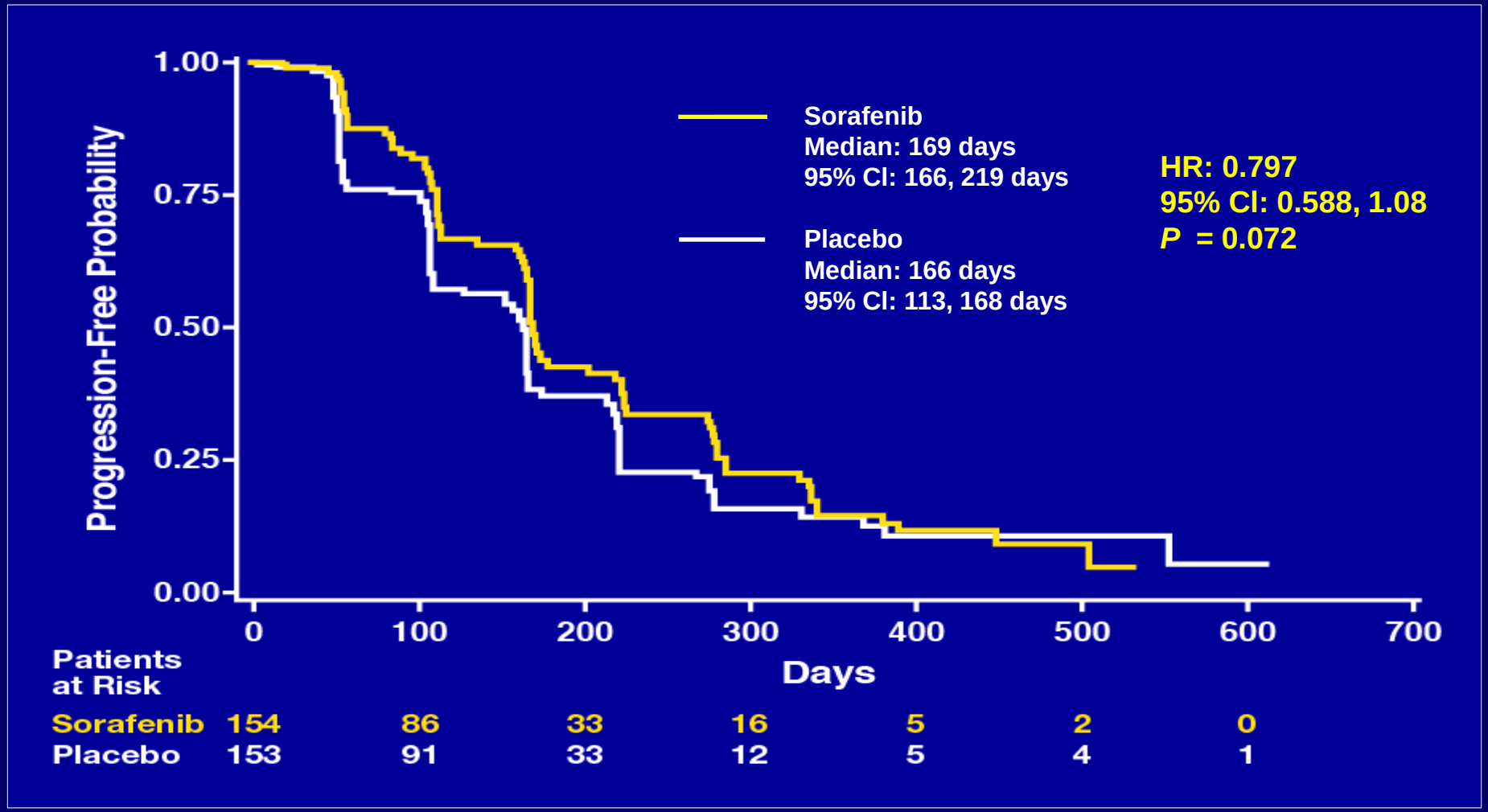
- TTP

Secondary Endpoints

- OS
- Time to VI/EHS
- Safety
- Others

Lencioni R et al. Presented at ASCO-GI 2012

SPACE Clinical Trial – Primary Endpoint: Time to Progression by Central Blinded Readers



Lencioni R et al. Presented at ASCO-GI 2012

Integrating Systemic and Loco-Regional Therapies in HCC: On-Going Phase 3 Studies

Acronym	Region	N	Endpoint	Experimental Arm	Control Arm	Est. Compl.
OPTIMA	Global	550	OS	RFA + ThermoDox	RFA	Nov. 2019
Hi-QUALITY	Americas – EU	520	OS	DEB-TACE	cTACE	Dec. 2022
ECOG 1208	US	400	PFS	TACE + sorafenib	TACE	Feb. 2018
TACE-2	Europe	412	PFS	DEB-TACE + sorafenib	DEB-TACE	N.A.
SIRveNIB	Asia-Pacific	360	OS	Y-90	sorafenib	Jul. 2015
SARAH	France	400	OS	Y-90	sorafenib	Dec. 2015
STOP-HCC	USA - EU	400	OS	Y-90 + sorafenib	sorafenib	Oct. 2016
SORAMIC	Europe	375	OS	Y-90 + sorafenib	sorafenib	Sep. 2014
YES-P	Global	328	OS	Y-90	sorafenib	Nov. 2017

www.clinicaltrials.gov