How to decide on the optimal algorithm for HCC?

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C. Verslype receives research grants from:

Bayer

Sirtex

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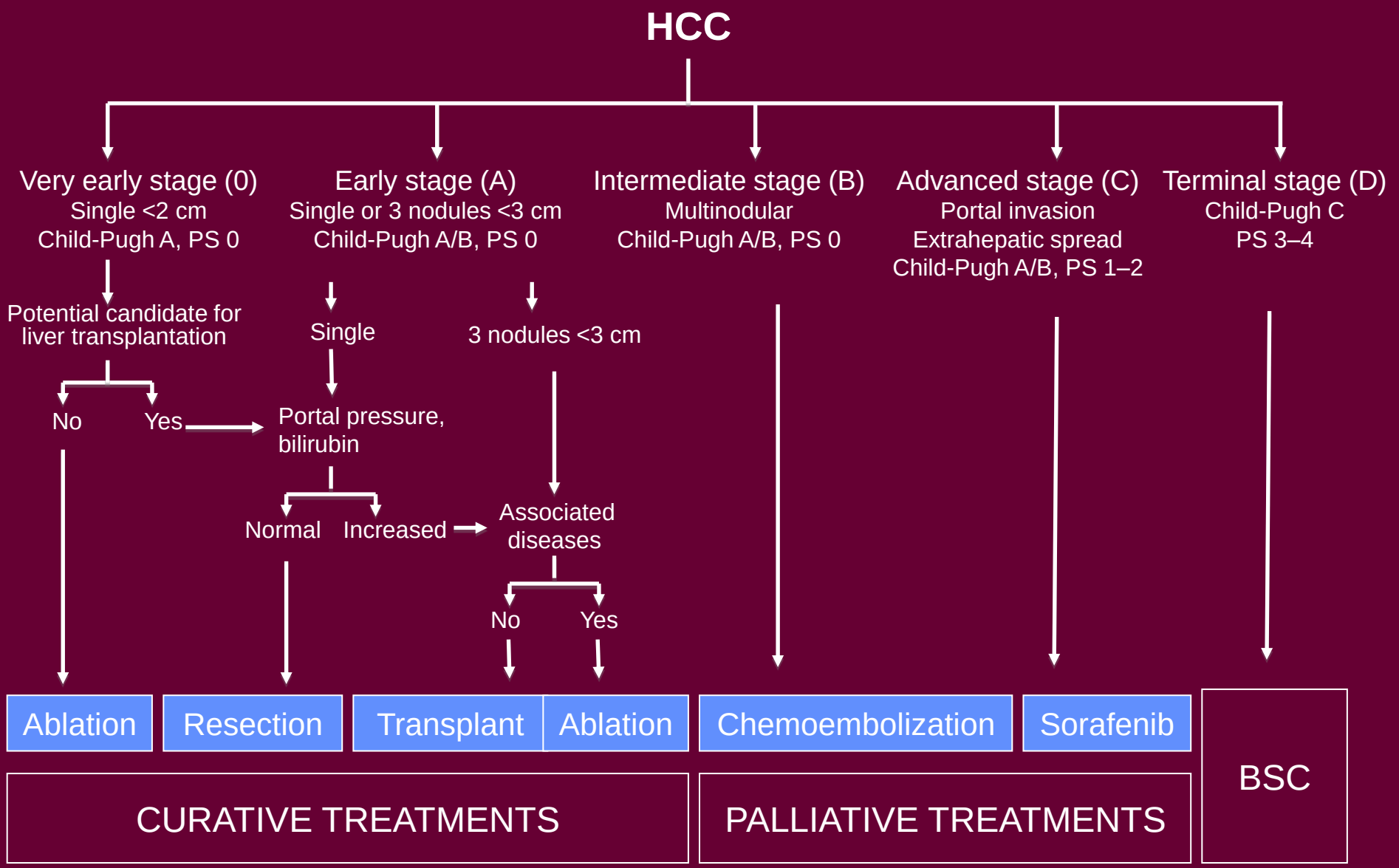
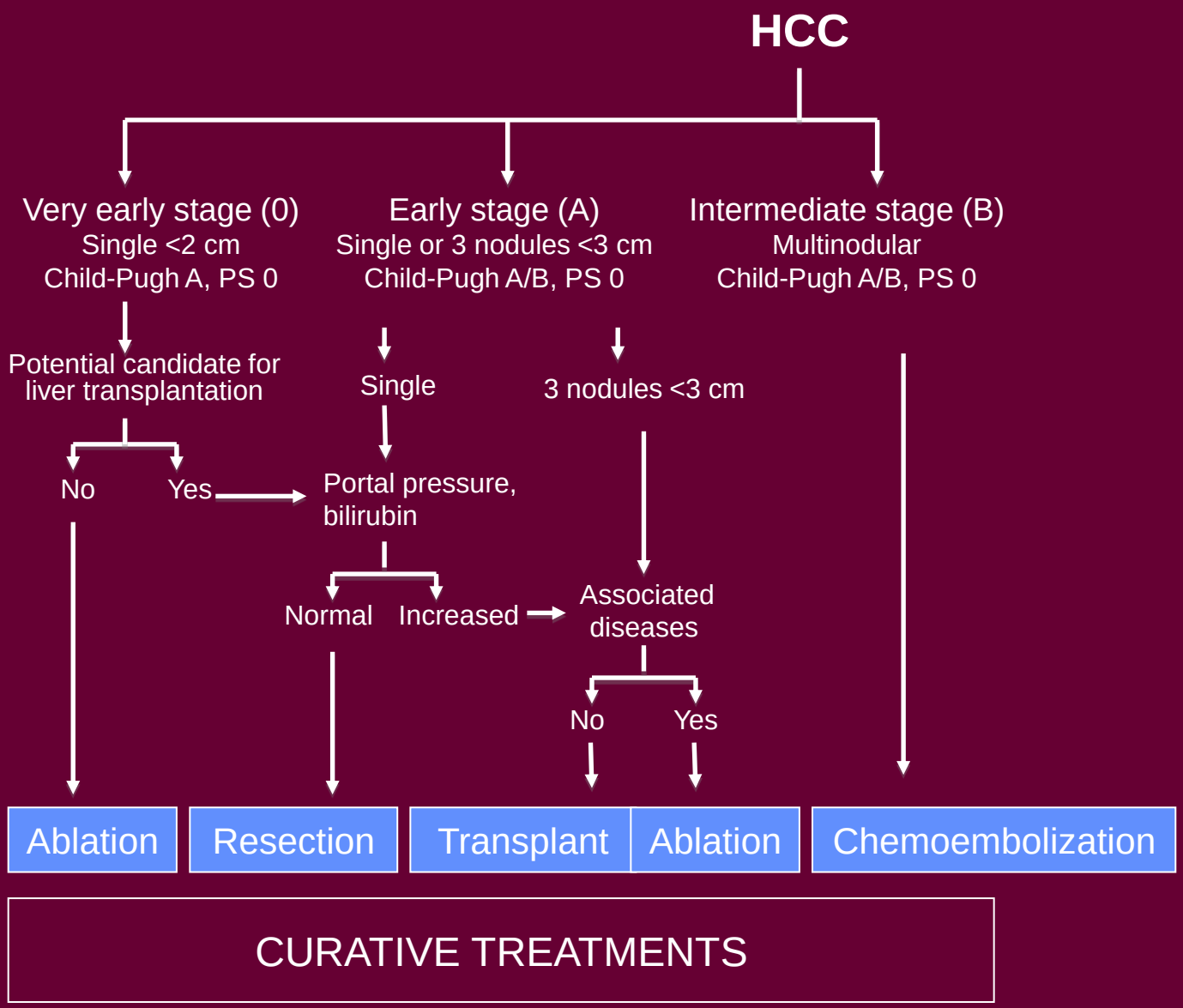
Pfizer

BCLC staging and treatment strategy



Forner, et al. Lancet. 2012 Mar 31;379(9822):1245-55. Rodriguez-Lope C, et al. J Hepatol. 2012;56 Suppl 1:S75-87.

BCLC staging and treatment strategy



CURATIVE TREATMENTS

Forner, et al. Lancet. 2012 Mar 31;379(9822):1245-55. Rodriguez-Lope C, et al. J Hepatol. 2012;56 Suppl 1:S75-87.

Following resection or ablation for early HCC

- 5 year recurrence rates > 70%
- Factors:
  - Microvascular invasion
  - Satellite tumours
  - Size and number of lesions
  - Poorly differentation
- How to reduce recurrence?
  - Liver transplantation
  - Sorafenib (STORM trial)?

STORM trial design

Stratification

- Region: Americas, Europe, Asia-Pacific
- Resection *vs* local ablation
- Child-Pugh A *vs* B7
- Intermediate *vs* high recurrence risk

Endpoints

- Primary: **RFS** (recurrence-free survival)
- Secondary: **TTR** (time to recurrence), **OS** (overall survival)
- Other: patient-reported outcomes, pharmacokinetics, biomarkers

Registered on ClinicalTrials.gov as NCT00692770
BID, twice daily; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation

Presented by: Jordi Bruix on behalf of the STORM Investigators

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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Key inclusion criteria

- New diagnosis of HCC with no extrahepatic spread or macrovascular invasion
- No residual disease present 3 to 7 weeks after resection or complete local ablation (RFA or PEI) confirmed by independent radiologic review
- No prior anti-cancer therapy for HCC
- Child-Pugh status A (5, 6) or B7 (no ascites)
- ECOG PS 0 with adequate bone marrow and renal function
- HCC with an intermediate or high recurrence risk

Risk of recurrence	Intermediate	High
Surgical resection[a]	All of the following: • Single tumor ≥2 cm • Well / moderately differentiated • Without microvascular invasion or satellite tumors	Single tumor any size and any of the following: • Microvascular invasion • Satellite tumors • Poorly differentiated *or* 2-3 tumors each ≤3 cm[a]
Ablation[b]	Single tumor 2-3 cm	Single tumor >3-5 cm *or* 2-3 tumors each ≤3 cm

[a]Defined by pathologic examination;
[b]Defined by imaging
ECOG PS, Eastern Cooperative Oncology Group performance status

Baseline characteristics (1 / 3)

Stratification factors, *n* (%)	Sorafenib (*n*=556)	Placebo (*n*=558)
Region		
Americas (North, South)	60 (10.8)	60 (10.8)
Asia-Pacific (inc. Australia, New Zealand)	330 (59.4)	330 (59.1)
Europe	166 (29.9)	168 (30.1)
Curative treatment		
Local ablation	106 (19.1)	108 (19.4)
Surgical resection	450 (80.9)	450 (80.6)
Risk of recurrence[a]		
Intermediate	298 (53.6)	308 (55.2)
High	258 (46.4)	250 (44.8)
Child-Pugh A		
5	429 (77.2)	432 (77.4)
6	112 (20.1)	106 (19.0)
Child-Pugh B		
7	15 (2.7)	16 (2.9)
8[b]	0	4 (0.7)

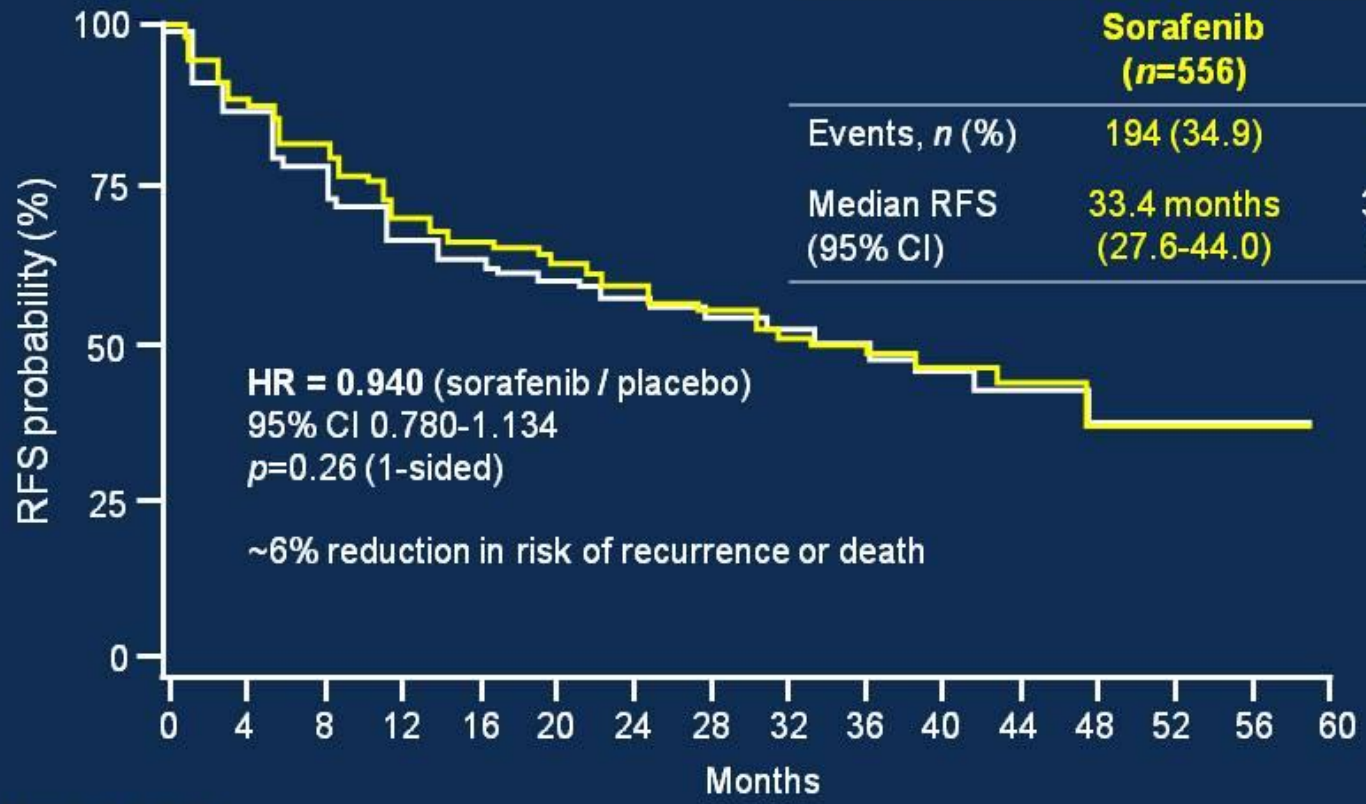
[a]*n*=2 patients with a low recurrence risk were included in the intermediate-risk group for the analysis;
[b]Protocol deviation

Baseline characteristics (3 / 3)

	Sorafenib (*n*=556)	Placebo (*n*=558)
Liver cirrhosis present, *n* (%)	357 (64.2)	344 (61.6)
Number of lesions, *n* (%)		
1	506 (91.0)	521 (93.4)
2	44 (7.9)	33 (5.9)
≥3	6 (1.1)	4 (0.7)
Maximum tumor size (mm), median (range)	35 (10-200)	35 (10-190)
Tumor satellites[a], *n* (%)		
No	408 (73.4)	411 (73.7)
Yes	42 (7.6)	39 (7.0)
Microscopic vascular invasion[a], *n* (%)		
No	304 (54.7)	303 (54.3)
Yes	146 (26.3)	147 (26.3)
Alpha fetoprotein (ng/mL)[b], *n* (%)		
≤200	418 (75.2)	404 (72.4)
>200	96 (17.3)	93 (16.7)

[a]Assessed only in the 450 patients in each group who underwent resection;
[b]Not available: *n*=42 sorafenib, *n*=61 placebo

RFS (independent review)



	Sorafenib (*n*=556)	Placebo (*n*=558)
Events, *n* (%)	194 (34.9)	270 (48.4)
Median RFS (95% CI)	33.4 months (27.6-44.0)	33.8 months (27.6-39.0)

Number at risk

Placebo	558	442	387	322	295	266	250	229	213	166	121	88	21	15	1
Sorafenib	556	349	298	244	221	192	172	153	135	102	70	50	6	4	1

CI, confidence interval

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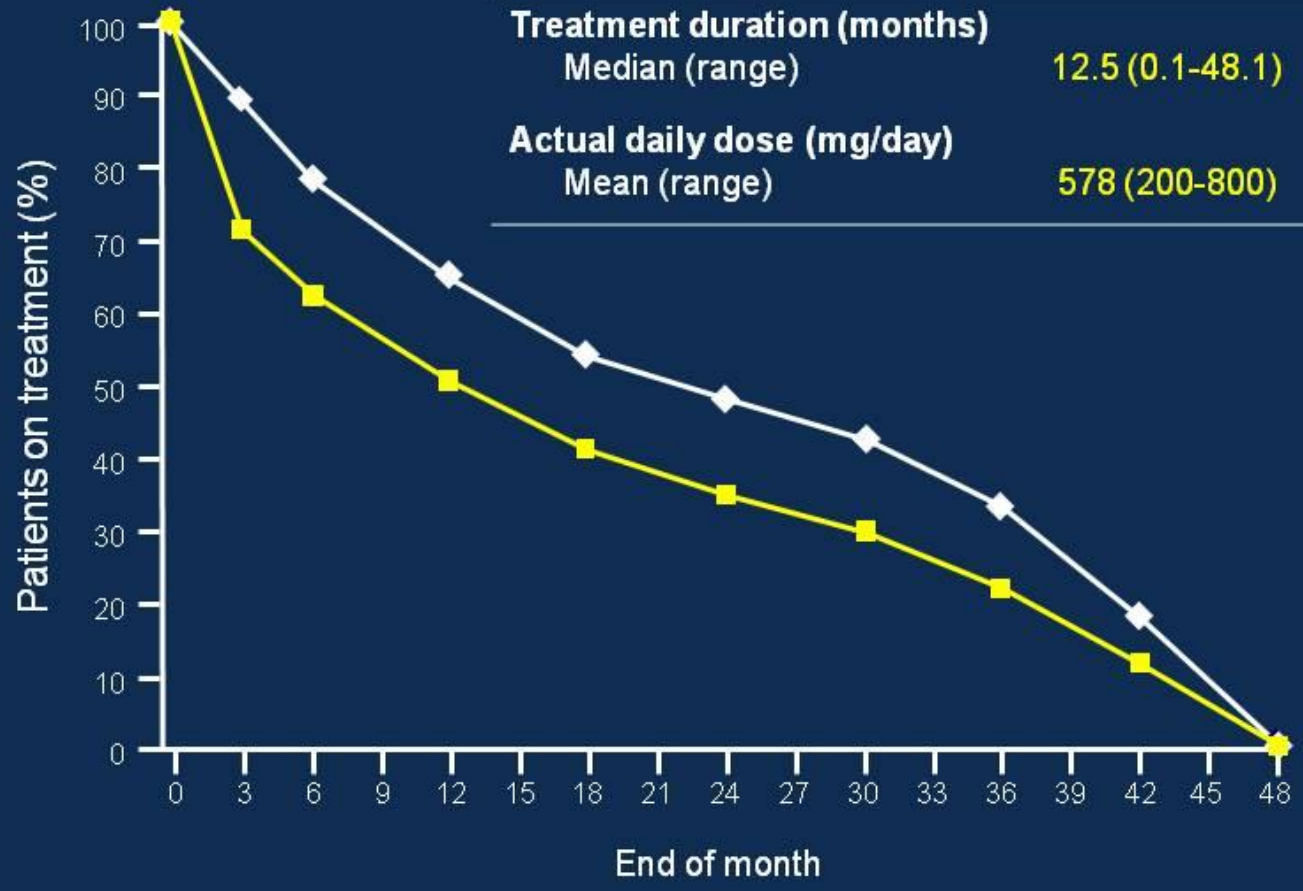
Primary reasons for treatment discontinuation

n (%)	Sorafenib (*n*=556)	Placebo (*n*=558)
Discontinued study drug[a]	471 (84.7)	447 (80.1)
Disease progression, recurrence, or relapse	165 (29.7)	274 (49.1)
Adverse event	133 (23.9)	41 (7.3)
Consent withdrawn	93 (16.7)	35 (6.3)
Completed all planned assessments (4 years)	35 (6.3)	65 (11.6)
Radiologic and clinical progression	8 (1.4)	8 (1.4)
Non-compliant with study medication	11 (2.0)	5 (0.9)
Death	10 (1.8)	5 (0.9)
Lost to follow-up	7 (1.3)	3 (0.5)
Protocol deviation	2 (0.4)	7 (1.3)
Other reasons	7 (1.3)	4 (0.7)

[a]As of the analysis cut-off date

Study drug administration

	Sorafenib (*n*=559)	Placebo (*n*=548)
Treatment duration (months)		
Median (range)	12.5 (0.1-48.1)	22.2 (0.1-49.2)
Actual daily dose (mg/day)		
Mean (range)	578 (200-800)	778 (223-808)



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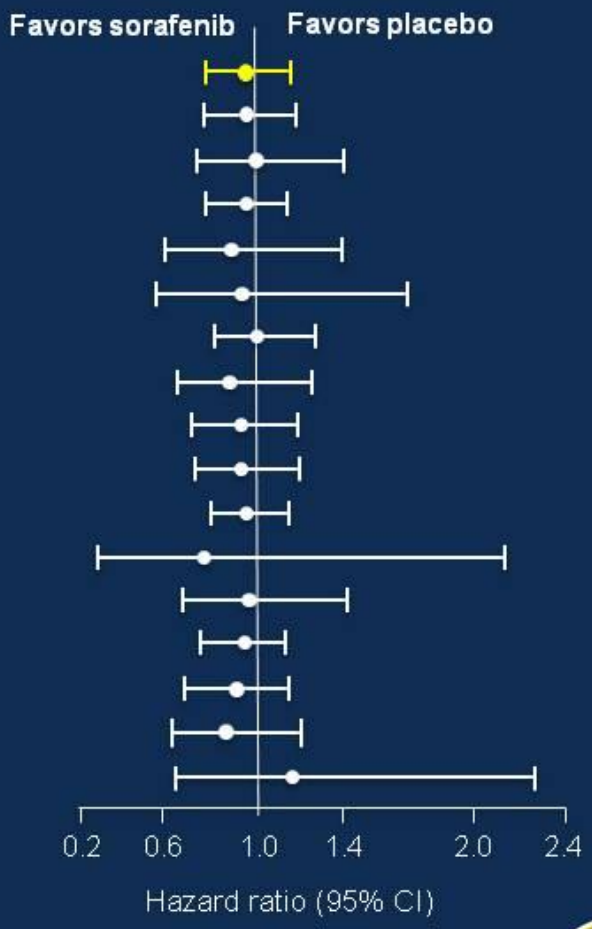
Subgroup analysis of RFS (independent review)

	N	HR (95% CI)
All patients (ITT)	1114	0.940 (0.780-1.134)
<65 years	744	0.942 (0.752-1.179)
≥65 years	370	1.007 (0.722-1.405)
Male	912	0.951 (0.777-1.165)
Female	202	0.887 (0.564-1.396)
Americas	120	0.931 (0.513-1.691)
Asia-Pacific	660	1.006 (0.792-1.277)
Europe	334	0.871 (0.617-1.230)
Intermediate risk	606	0.926 (0.710-1.209)
High risk	508	0.933 (0.721-1.207)
Child-Pugh A	1079	0.954 (0.791-1.152)
Child-Pugh B	35	0.760 (0.270-2.141)
Local ablation	214	0.970 (0.656-1.434)
Surgical resection	900	0.937 (0.759-1.156)
Hepatitis B	561	0.900 (0.695-1.166)
Hepatitis C	297	0.849 (0.601-1.199)
Alcohol use	109	1.183 (0.614-2.280)



ITT, intention to treat

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Overall survival

	Sorafenib (*n*=556)	Placebo (*n*=558)
Events, *n* (%)	102 (18.3)	115 (20.6)
Median OS	Not reached	Not reached

HR = 0.995 (sorafenib / placebo)
95% CI 0.761-1.300
p=0.48 (1-sided)[a]

Number at risk

Placebo	558	540	520	504	477	450	433	420	403	381	298	212	134	78	29	5
Sorafenib	556	503	482	460	445	419	395	383	367	340	251	176	110	62	21	5

[a]First planned OS interim analysis alpha = 0.000449 (1-sided)

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Conclusions

- The STORM trial of adjuvant sorafenib after curative resection or ablation of HCC did not meet its primary endpoint of improving RFS
  - HR = 0.940; 95% CI 0.780-1.134; *p*=0.26 (1-sided)
  - Median RFS was 33.4 and 33.8 months for sorafenib and placebo, respectively
  - No improvement in either TTR or OS
  - Treatment duration was shorter in the sorafenib group (median 12.5 *vs* 22.2 months)
- Adverse events were consistent with the known safety profile of sorafenib in HCC

Decision making process on the waiting list for OLT: AIMS

1. Prevent drop-out while on the list
2. Prevent recurrence following transplantation
3. Prevent mortality in all patients (from the time of listing)

Decision making process on the waiting list for OLT: METHODS

1. **E**stimate risk of drop-out
2. **S**elect the treatment with the most optimal risk-benefit
3. **M**easure the response and monitor complications
4. **O**bserve durability of response

Decision making process on the waiting list for OLT: METHODS

1. Estimate risk of drop-out
   - *Listing criteria (no waiting time = no drop-out)*
   - *Natural history*
2. Select the treatment with the most optimal risk-benefit
3. Measure the response and monitor complications
4. Observe durability of response

Eurotransplant listing criteria for HCC

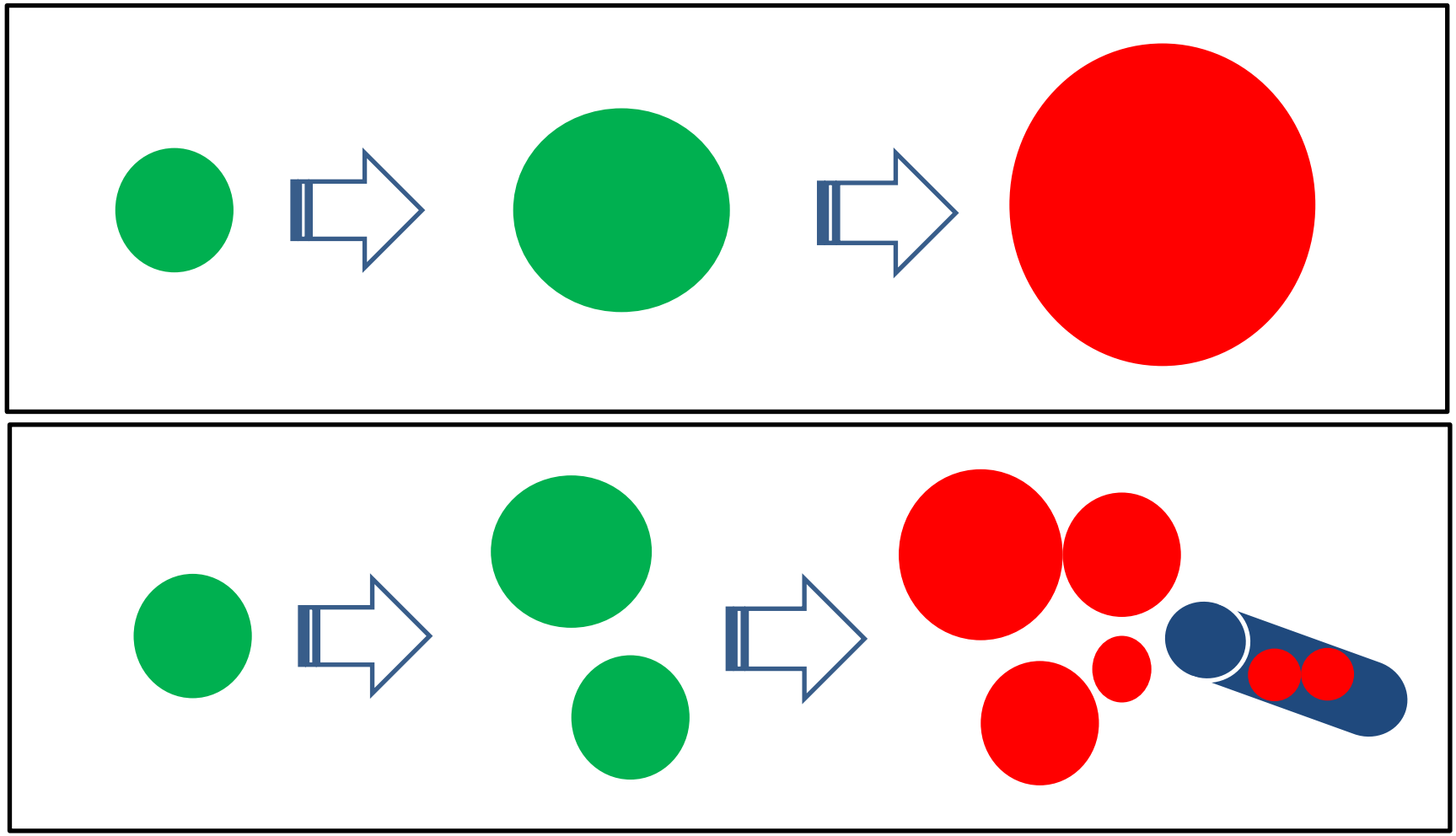
N°	Listing criteria	A	B/L	G	NL	SLO	CRO
	Accepted ways of diagnosis of initial HCC (1 or more possible)	O	O	O	O	O	O
1a	Biopsy	✓	✓	✓	✓	✓	✓
1b	AFP >400 ng/ml and one positive result with hypervascularisation with imaging technique (Spiral-CT, MRI, Angiography)	✓	✓	✓	✓	✓	✓
1c	Two positive results with hypervascularisation with imaging technique (Spiral-CT, MRI, Angiography). Two different techniques must be applied	✓	✓	✓	✓	✓	✓

N°	exceptional MELD criteria	A	B/L	G	NL	SLO	CRO
	Patient fulfills the Milan criteria at the time of request, one from 2a or 2b and both 3 and 4 have to be met	O	O	O	O	O	O
2a	Recipient has one tumor ≥2 and <5 cm in diameter	✓	✓	✓	✓	✓	✓
2b	Recipient has ≤3 tumors each <3 cm in diameter	✓	✓	✓	✓	✓	✓
3	Recipient has no extrahepatic metastases	✓	✓	✓	✓	✓	✓
4	Recipient has no macrovascular invasion	✓	✓	✓	✓	✓	✓

N°	Exclusion criterion	A	B/L	G	NL	SLO	CRO
	Recipients with lesion(s) initially, and also after downstaging, outside the Milan criteria.	✓	✓	✓	✓	✓	✓

Eurotransplant Manual© – version 4.1; May 28, 2013

Natural history of HCC



Intention-to-treat Outcome of T1 Hepatocellular Carcinoma Using the Approach of "Wait and not Ablate" until Meeting T2 Criteria for Liver Transplant Listing

- More insights in natural history of HCC < 2 cm (T1)
- 114 patients "wait and not ablate" approach with serial CT or MRI every 3 months until meeting T2 criteria (1 lesion 2-5 cm or 2-3 lesions ≤3 cm)
- Mean diameter increase: 0.4 cm/3 months
- Rapid tumor progression (> 1 cm/ 3 months) in 20%
- 10% risk of exclusion from LT due to progression beyond Milan at 2 years

Mehta et al., AASLD 2013

Basic pathology of small HCC

- HCC nodules < 1.5 cm are uniformly well differentiated

- HCC nodules between 1.5 and 2.0 cm in diameter often contain zones of less differentiated tissue with more intense proliferative activity
  - portal microinvasion in 10% of the cases
  - microsatellites in 3% of the cases, usually within 1.0 cm of the main tumor

Kojiro 1999, Maeda 2000, Kojiro 2002, Nakashima 2003

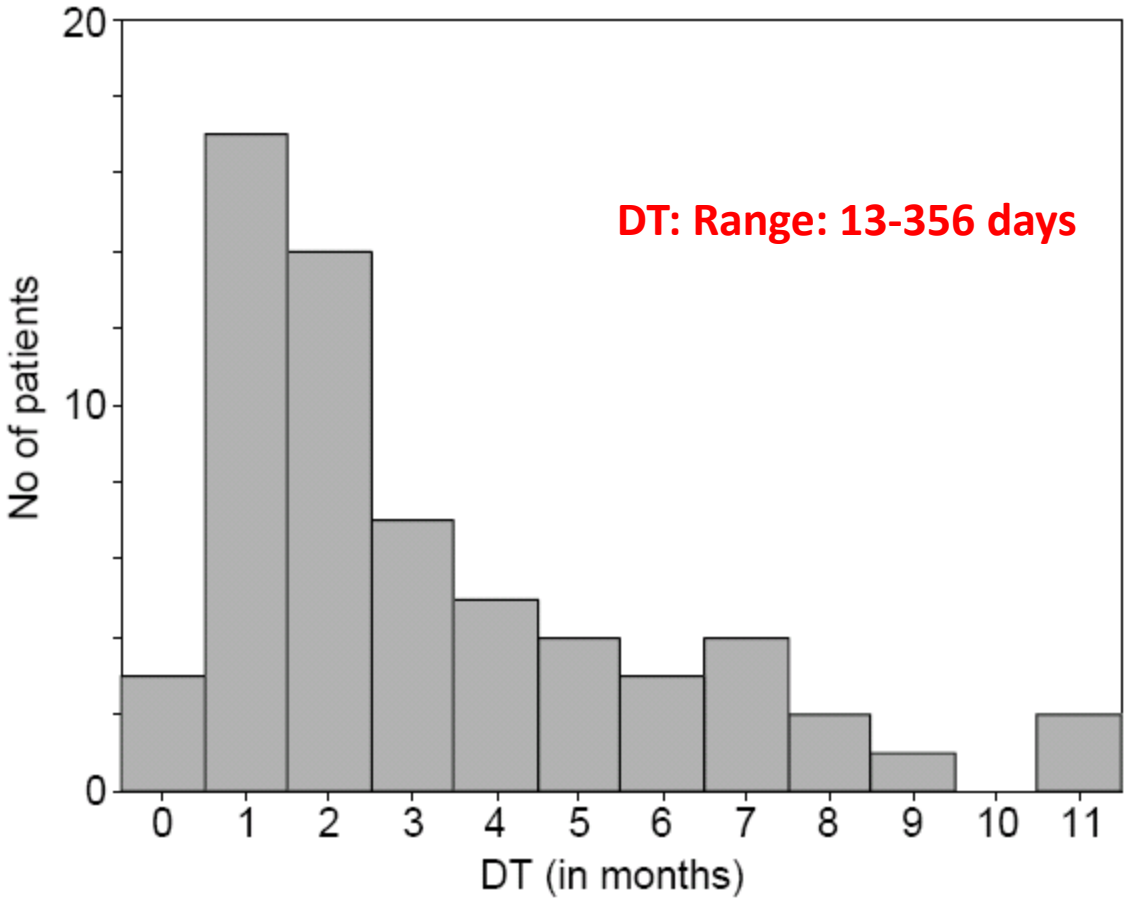


Fig. 1. Distribution of the doubling time (DT) of the tumors in the 62 patients studied.

Cucchetti et al. J Hepatol 2005

Tumour biology

- Real-time observation (“Test of time”)
- Doubling time variable
- Beyond 1.5 cm more advanced HCC
- AFP: surrogate marker for poor differentation
  - Cut-off value? Evolution?
- Role of FDG-PET?

Probability of drop-out from the waiting list (without therapy)

OUT

< 20% at 6 months

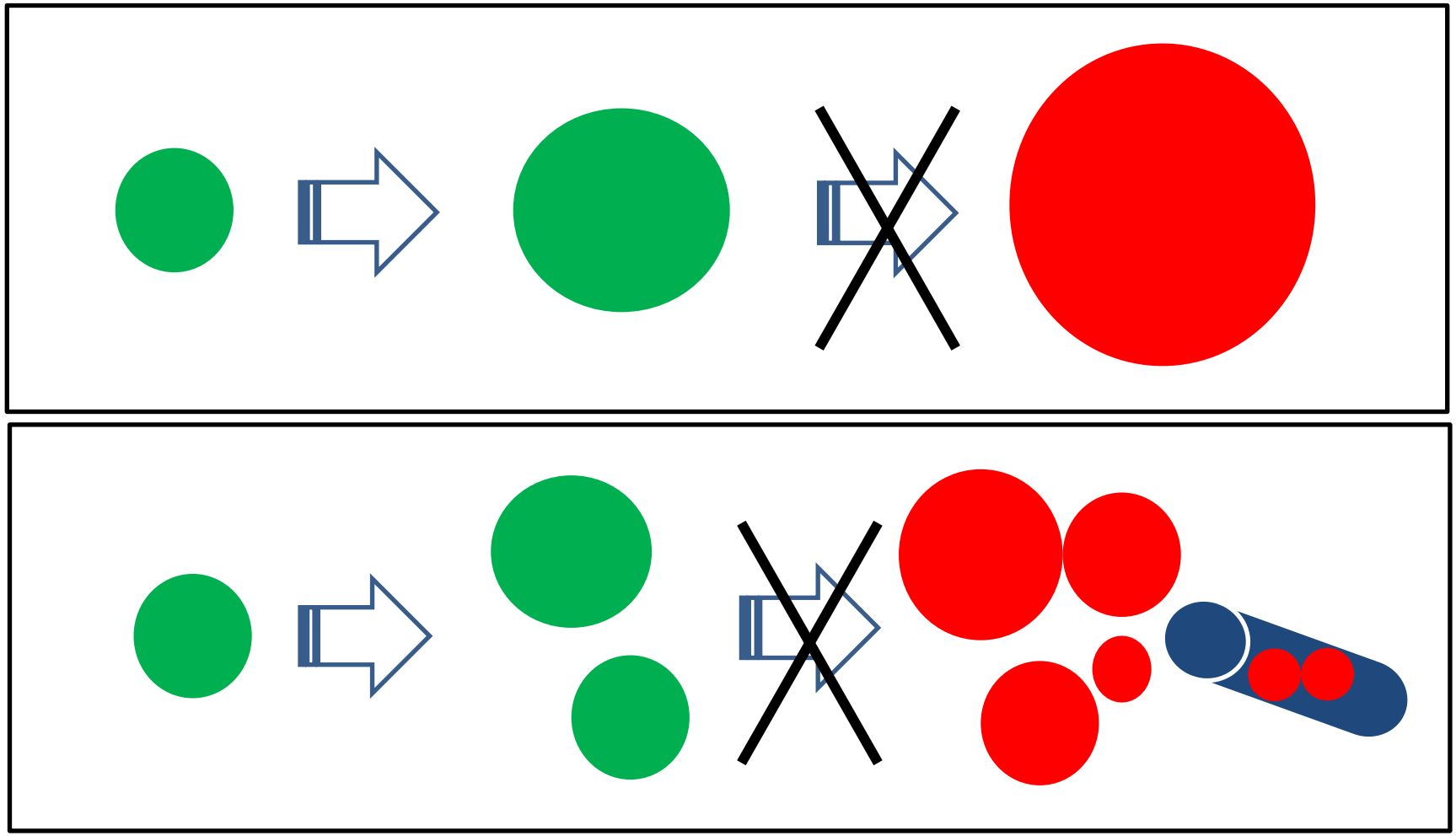
< 40 % at 12 months

Llovet et al. Hepatology 1999; Yao JF et al. Liver Transpl 2002; Freeman RB Jr. et al. Liver Dis 2007; Pelletier et al. Liver Transpl 2009; Pompili M et al. WJG 2013

Decision making process on the waiting list for OLT: METHODS

1. Estimate risk of drop-out
2. **Select the treatment with the most optimal risk-benefit**
3. Measure the response and monitor complications
4. Observe durability of response

Prevention of drop-out



Guidelines “2012”

1. No randomized controlled trials

2. International consensus conference 2010: bridging therapy is recommended, however no recommendation can be made for preferring a specific locoregional therapy *

3. EASL-EORTC Clinical Practice Guidelines: it is recommended to treat patients waiting for transplant with local ablation and as second choice with chemoembolization when waiting times are estimated to exceed 6 months **

*** Clavien et al. Lancet Oncol 2012**

**** J Hepatol 2012 and Eur J Cancer 2012**

Studies on RFA as bridging therapy

Reference	N (criteria)	Bridging therapy	Median waiting time	Drop-out rate (%)	Recurrence after LT	Survival (intention to treat)	Survival (after LT)
Mazzafero (2004)	50 MC (80%)	RFA	9.5 mo	0	2 (4%)	NA	83 % (3 yr)
Lu (2005)	52 MC (81%)	RFA	12.7 mo	6 (12%)	0	74% (3 yr)	76 % (3 yr)
Du Bay (2011)	77 MC	RFA	9.5 mo	19 (25%)	1 (2%)	NA	80% (3 yr)

Retrospective studies on TACE as bridging therapy

Reference	N (criteria)	Bridging treatment	Median waiting time	Drop-out rate (%)	Recurrence after LT	Survival (intention to treat)	Survival (after LT)
Graziadei (2003)	48 MC	TACE	6 mo	0	1 (2.4%)	94% (5 yr)	94% (5 yr)
Hayashi (2004)	20 MC	TACE	11 mo	6 (35%)	NA	61% (3 yr)	100% (4 yr)
Maddala (2004)	54 MC (87%)	TACE	7 mo	25% at 12 mo	5 (13.3%)	61 % (5 yr)	74% (5 yr)
Alba (2008)	63 MC	TACE	6.5 mo	7 (11%)	6 (10.7 %)	NA	60.4% (5 yr)

Performance of loco-regional treatments: the amount of tumoral necrosis?

Sustained Complete Response and Complications Rates After Radiofrequency Ablation of Very Early Hepatocellular Carcinoma in Cirrhosis: Is Resection Still the Treatment of Choice?

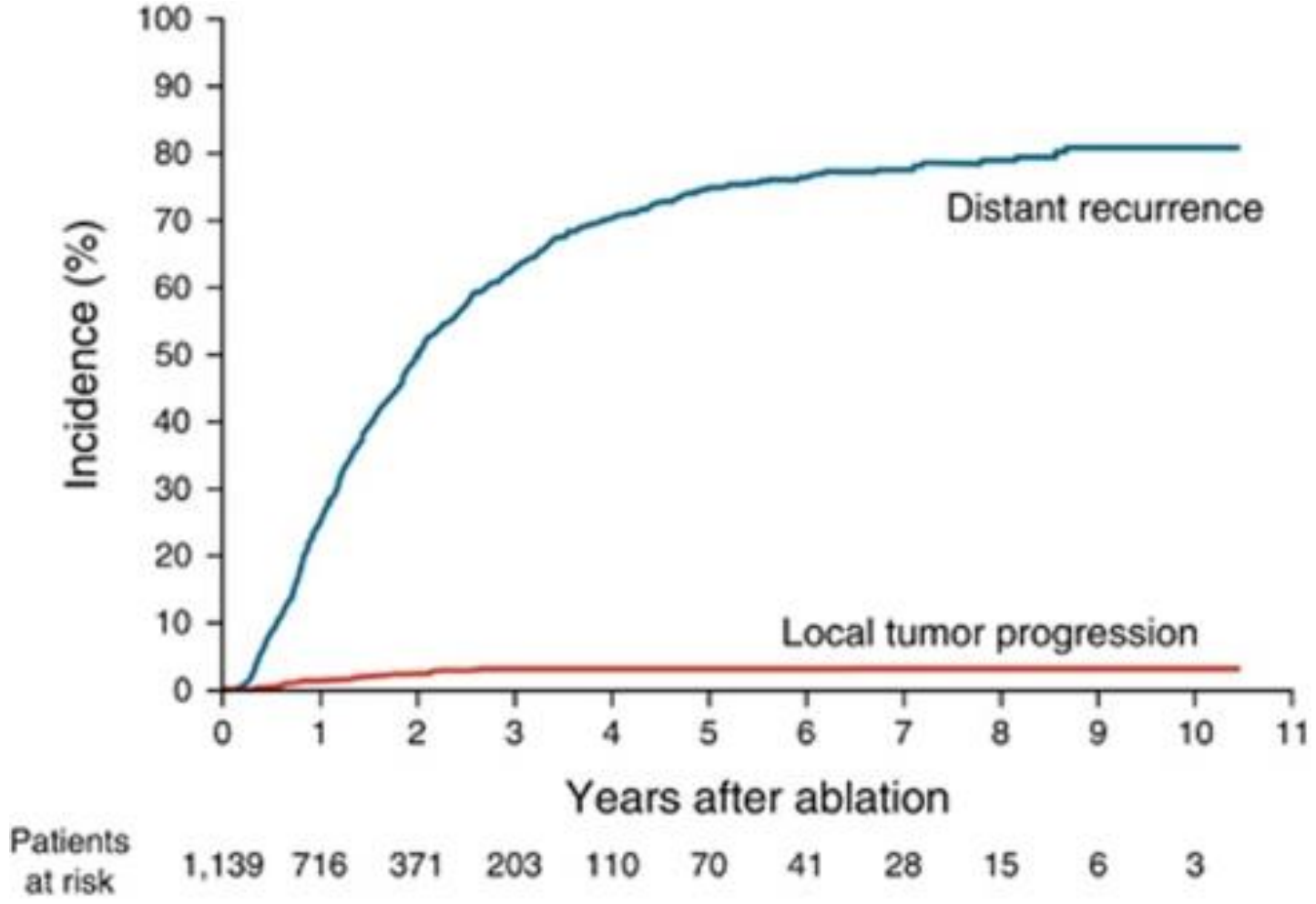
Tito Livraghi,[1] Franca Meloni,[1] Michele Di Stasi,[2] Emanuela Rolle,[3] Luigi Solbiati,[4] Carmine Tinelli,[5] and Sandro Rossi[6]

Sustained complete response (218 patients):

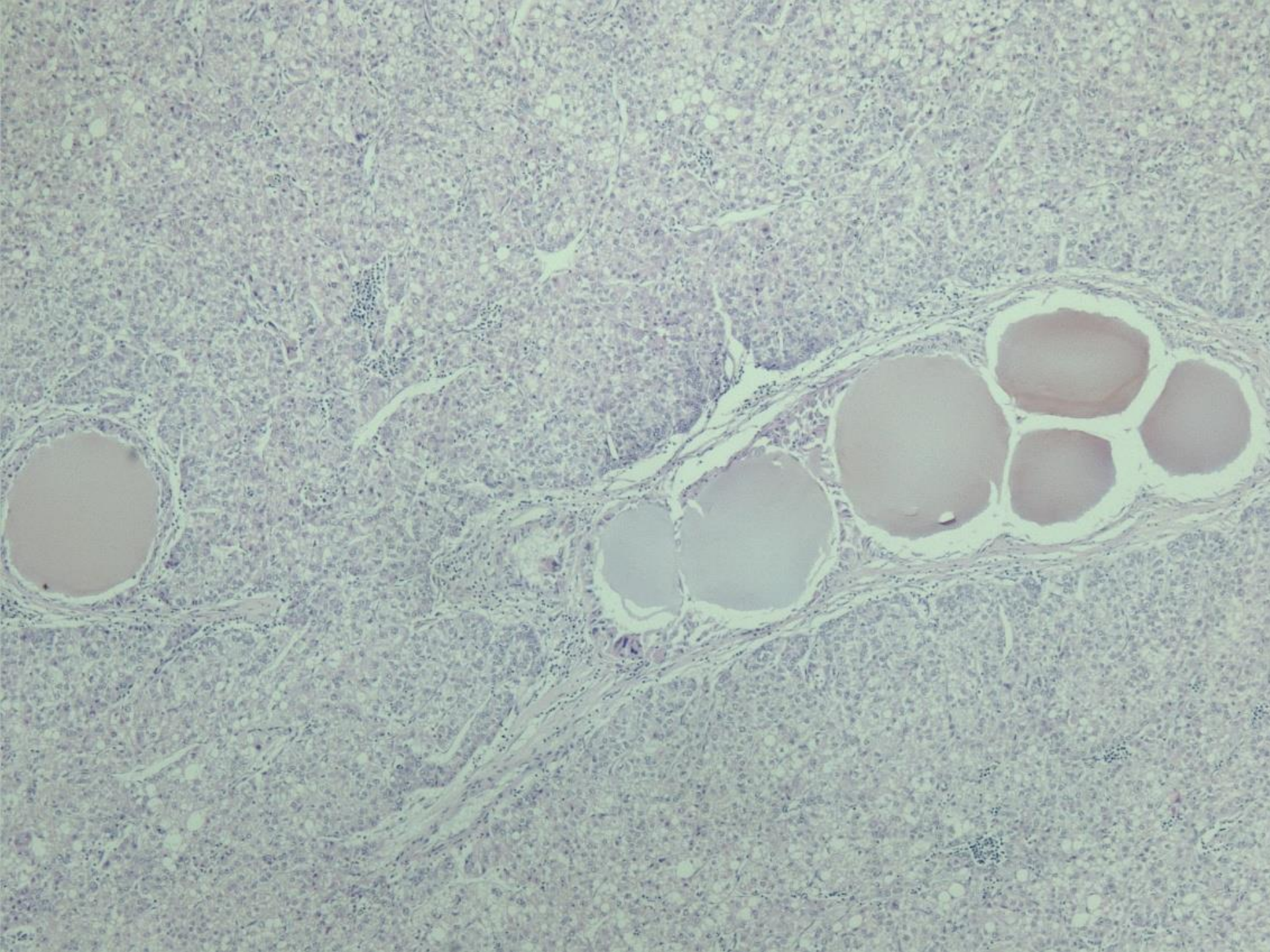
97% after a median follow-up of 31 months

Hepatology 2008; 47: 82–89

Radiofrequency ablation for biopsy proven HCC: 10-year outcome



Shiina S et al. Am J Gastroenterol 2012



Efficacy of Selective Transarterial Chemoembolization in Inducing Tumor Necrosis in Small (<5 cm) Hepatocellular Carcinomas

Rita Golfieri,[1] Alberta Cappelli,[1] Alessandro Cucchetti,[2] Fabio Piscaglia,[3] Maria Carpenzano,[1] Eugenia Peri,[2] Matteo Ravaioli,[2] Antonia D'Errico-Grigioni,[4] Antonio Daniele Pinna,[2] and Luigi Bolondi[3]

	% Necrosis
Lesions < 2 cm	59,6 %
Lesions 2,1 - 3 cm	68,4 %
Lesions > 3 cm	76,2 %
- Superselective TACE	91,8%*
- Lobar TACE	66,5 %

* p = 0.038

Golfieri et al. Hepatology 2011

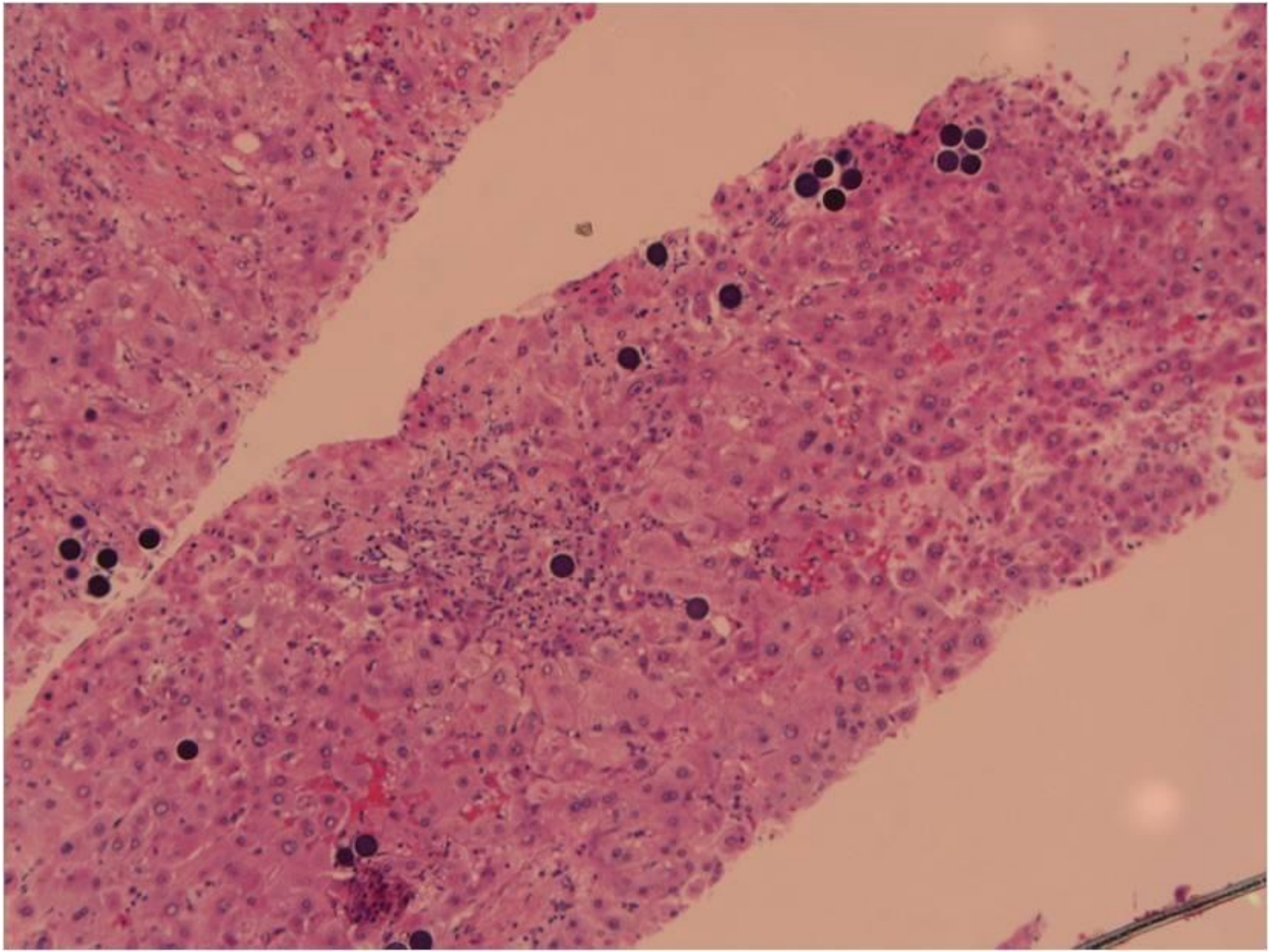


Table 6. Histologic Necrosis Stratified According to Pretreatment Size

	n (%)			
Pretreatment Size	**1–2.9 cm**	**3–5 cm**	**>5 cm**	***P* Value**
Total number	9/38 (24)	17/38 (45)	12/38 (31)	
Histologic necrosis, n (%)				
100%	8 (89)	11 (65)	4 (33)	0.199
>50%	1 (11)	2 (12)	6 (50)	
<50%	0 (0)	4 (23)	2 (17)	

Riaz, Hepatology 2009

Table 4. Histologic Necrosis Stratified According to Time Period between First Treatment and Explantation

Time from Treatment	<3 Months	3–6 Months	>6 Months	*P* Value
Total number	11/38 (29)	8/38 (21)	19/38 (50)	
Number of treatments to target lesion, median (range)	1 (1–2)	1 (1–2)	1 (1–2)	
Histologic necrosis, n (%)				
100%	4 (36)	6 (75)	13 (68)	0.015
>50%	1 (9)	2 (25)	6 (32)	
<50%	6 (55)	0 (0)	0 (0)	

Riaz, Hepatology 2009

Decision making process on the waiting list for OLT: METHODS

1. Estimate risk of drop-out
2. Select the treatment with the most optimal risk-benefit
3. **Measure the response (or define failure) and monitor complications.**
4. Observe durability of response

Radiological-histological correlation of locoregional therapies

- 128 pts, 55 days median waiting time for LT
- Pre-LT imaging (N, size, response):
  - correct in 57% of patients
  - understaging: 38%
  - overestimated tumor stage: 5%
- Outcome (3 yr OS and DFS):
  - Complete necrosis: 100 % and 100%
  - Partial necrosis: 78% and 75 %

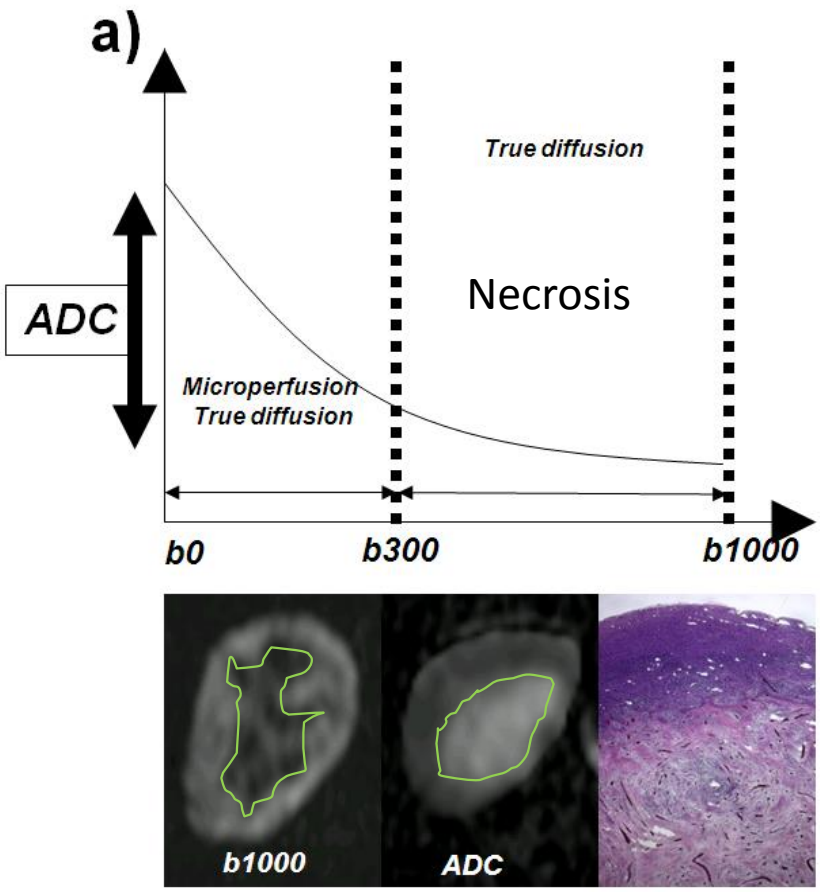
Galal et al. HBP Dis Int 2013

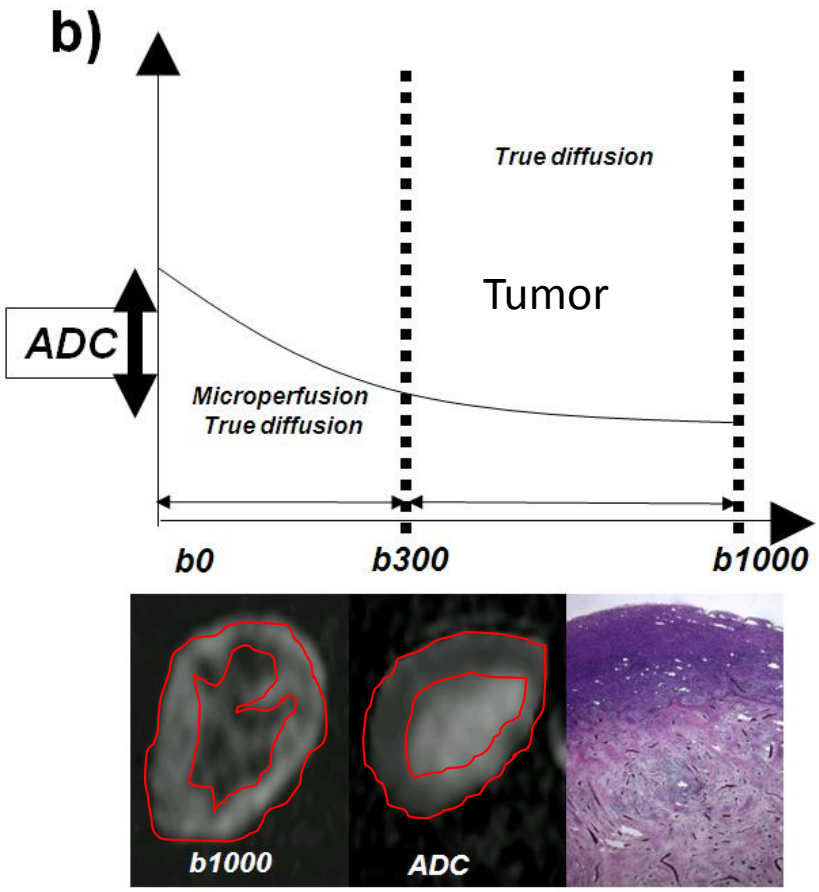
Chemoembolization for Hepatocellular Carcinoma: 1-Month Response Determined with Apparent Diffusion Coefficient Is an Independent Predictor of Outcome[1]

Vincent Vandecaveye, MD, PhD
Katrijn Michielsen, MSc
Frederik De Keyzer, MSc
Wim Laleman, MD, PhD
Mina Komuta, MD, PhD
Katya Op de Beeck, MD
Tania Roskams, MD, PhD
Frederik Nevens, MD, PhD
Chris Verslype, MD, PhD
Geert Maleux, MD, PhD

Radiology 2014

Diffusion-weighted MRI

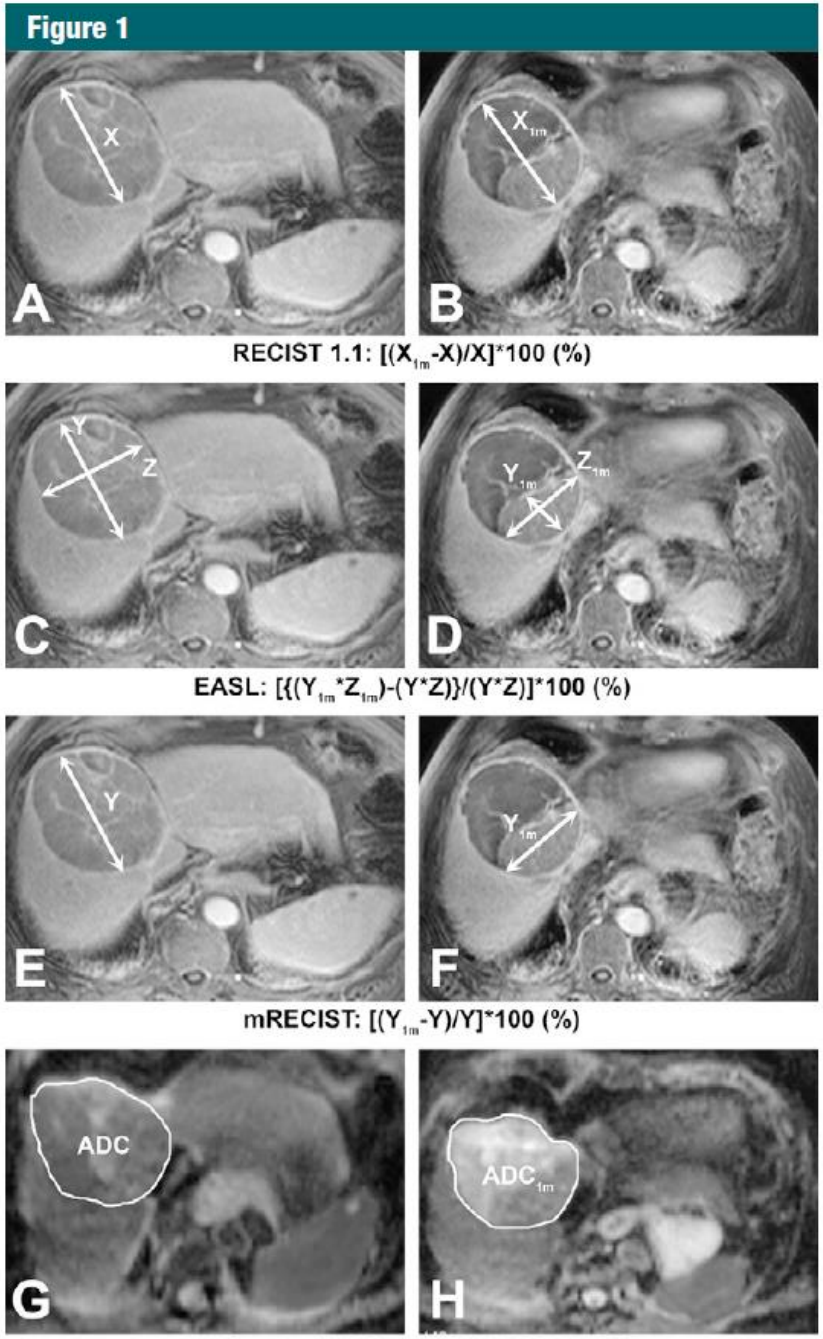




Methods

- Study of 40 patients
- MRI prior and 1 month following TACE
- Response assessment:
  - RECIST
  - EASL
  - mRECIST
  - ADC-ratio
- Relation between response assessment and progression free survival

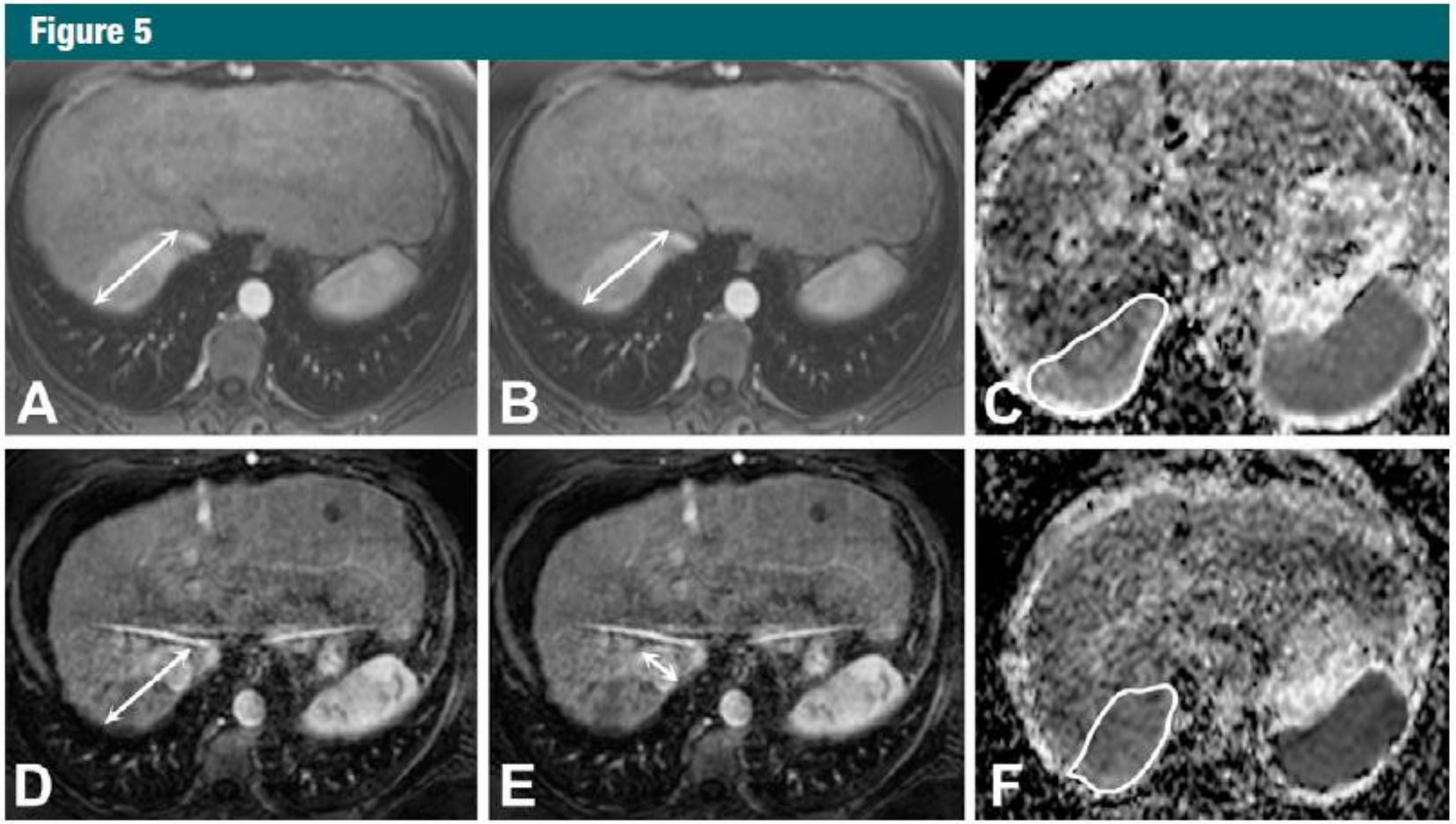
Vandecaveye et al. Radiology 2014



Vandecaveye et al. Radiology 2014

Patient with short progression free survival (4 months)

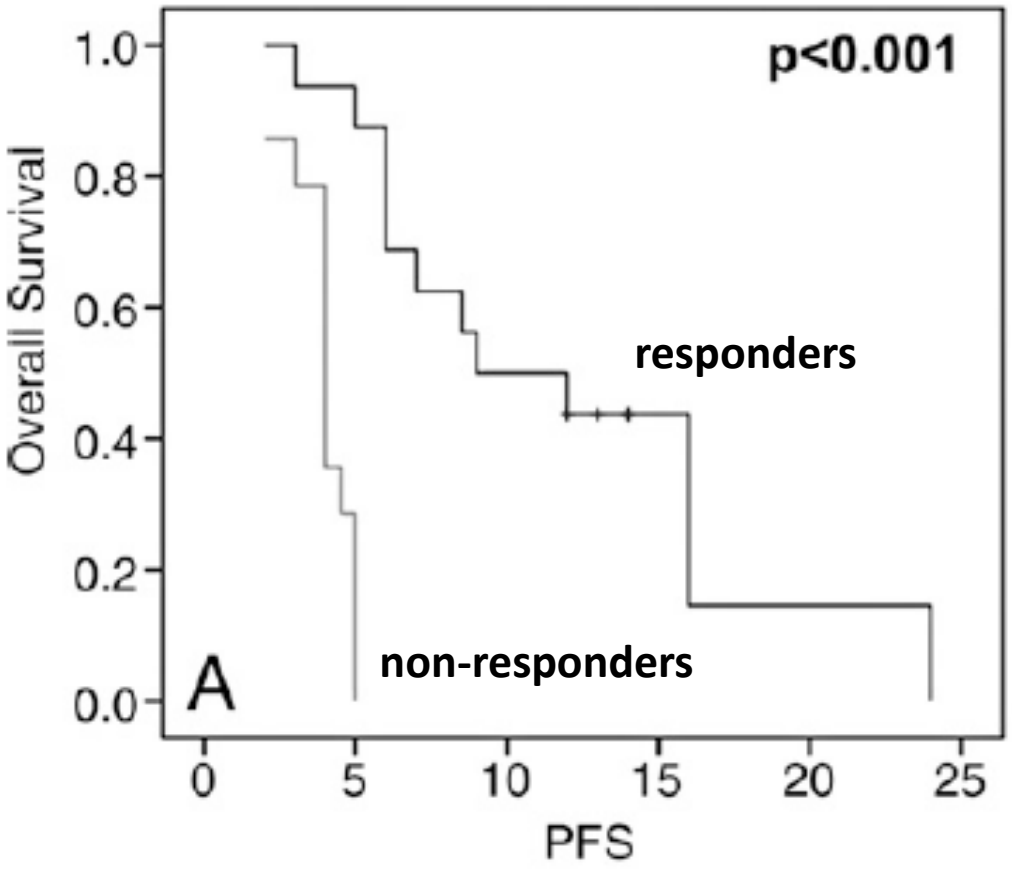
RECIST **mRECIST** **ADC**



SD **PR** **PD**

Vandecaveye et al. Radiology 2014

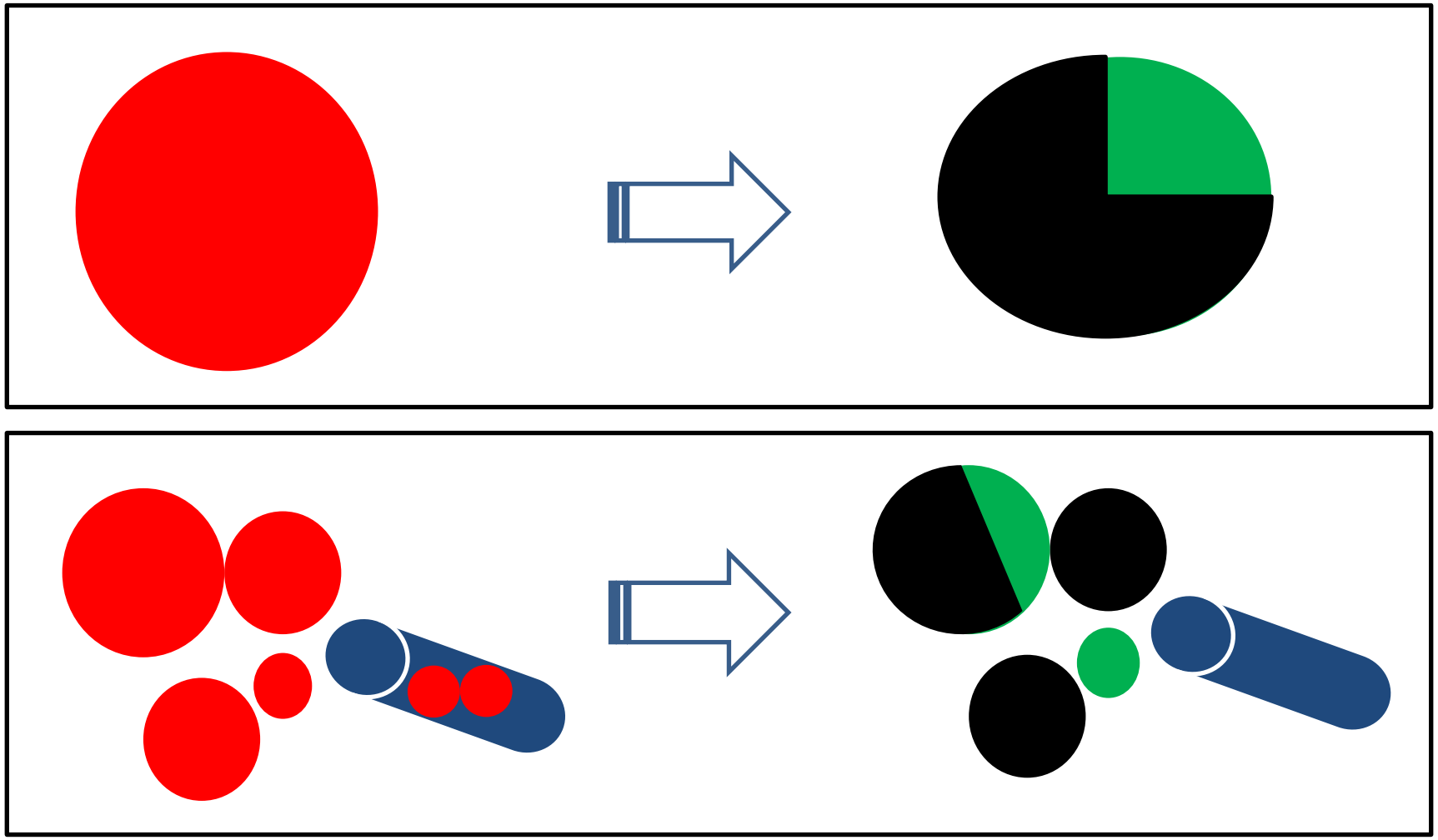
1-month ADC-ratio after initial TACE and progression free survival



RECIST, mRECIST, EASL: not significant

Vandecaveye et al. Radiology 2014

Downstaging of HCC



OUT IN

Downstaging of HCC beyond conventional liver transplantation criteria

Ref.	N (criteria)	Bridging treatment	Down-staged	Trans-plant	Recurrence free survival after LT	ITT Survival	Survival (after LT)
Yao (2008)	61 > MC, UCSF	TACE, RFA, resection	43/61 (71%)	35 (67%)	92% at 2 yr	69% at 4 yr	92% at 2 year
Jang (2010)	386 > MC	TACE	160/386 (41.5%)	37 (10 %)	66.3 % at 5 yr	NA	54.6% at 5 yr

Poor outcome: no response to therapies
high AFP (> 400 ng/ml, rise in AFP > 15 ng/ml/months*

* Vibert et al. Am J Transplant 2010

Performance of TARE vs. TACE in downstaging HCC

Table 1. Comparison of TARE Versus TACE.

TARE vs. TACE	Lewandowski et al. (7)N = 43 vs. 35	Carr et al. (8)N = 99 vs. 691	Kooby et al.‡ (9)N = 27 vs. 44	Salem et al. (10)N = 123 vs. 122
Median OS (months)	35.7 vs. 18.7; $P = 0.18$	11.5 vs. 8.5;$P < 0.05$*	6 vs. 6; $P = 0.74$	20.5 vs. 17.4;$P = 0.23$
Radiographic response:				
WHO Response (%)	61 vs. 37; $P = 0.12$	41 vs. 60†	11 vs. 6; $P = 0.73$§	49 vs. 36; $P = 0.10$
T3 to T2 (%)	58 vs. 31; $P = 0.023$	N/A	N/A	N/A
TTP (months)	33.3 vs. 12.8; $P = 0.005$	N/A	N/A	13.1 vs. 8.4;$P = 0.023$
Tolerability		N/A		
Median hospitalization (days)	0 vs. 2; $P < 0.001$		1.7 vs. 5.0; $P = 0.05$	0 vs. 1.8; $P < 0.001$
Any complication (%)			44 vs. 70; $P = 0.05$	
Hyperbilirubinemia (%)	Grade 3/4: 26 vs. 7		>3 mg/dL: 4 vs. 16;$P = 0.1$	

*OS between ^{90}Y and TACE became nonsignificant after adjusting for baseline bilirubin, presence of PVT, and baseline AFP level.

†Single dose of TARE to lobe with dominant disease burden; 43% bilobar in TARE. TACE q 8-10 weeks.

‡Sir-Spheres

§Radiographic response by RECIST at 3 months.

Lewandowski et al. Am J Transplant 2009
Carr et al. Cancer 2010
Kooby et al. J Vasc Interv Radiol 2010
Salem et al. Gastroenterology 2011

Decision making process on the waiting list for OLT: METHODS

1. Estimate risk of drop-out
2. Select the treatment with the most optimal risk-benefit
3. Measure the response and monitor complications
4. **Observe durability of response**

Sorafenib as bridging therapy?

Ref.	N	Study design	Safety	Efficacy
Vouche M et al. Hepatology 2013	7 SOR, 9 no-SOR	prospective, randomized, combination with Y90	Not reported.	SOR did not augment radiologic of pathologic response to Y90. No dropout or survival data reported.
Frenette CT et al. Transpl Int 2013	15 SOR, 64 no-SOR	retrospective	Same rate of complications	same drop out rate same OS
Truesdale AE et al. Transpl Int. 2011.	10 SOR, 23 no-SOR	retrospective	Increased rate of acute cellular rejection and biliary complications (67% vs. 22%)	Overall survival unchanged
Borentain P et al. Clin Res Hepatol Gastroenterol. 2011	1	case report	No complications	Complete necrosis, no survival data
Saidi RF et al. Clin Res Hepatol Gastroenterol. 2011	7	case series	1 re-OLT	1 recurrence

Courtesy: J. Benckert – T. Berg, Leipzig, GE

Conclusions – research agenda

- Recurrence of HCC following locoregional treatments is the rule and sorafenib is not of any help
- We know little on the most appropriate management of patients on the waiting list for liver transplantation, despite the availability of many therapies
- The success of bridging on the intention-to-treat survival of patients depends on
  - the tumour biology
  - the response to the therapy (extent and durability)
- Current unmet needs for management of patients on the waiting list:
  - tools to assess tumour biology
  - early assessment of a maintained response to therapy