SIRT FOR LIVER CANCER

SIRTEX Lunch Symposium, Cebu, 23 Nov 2013

Dr. Stephen L. Chan
Department of Clinical Oncology
The Chinese University of Hong Kong

Outline

I will not talk on

- Mechanism of SIRT
- Data on efficacy of SIRT
- Epidemiology of HCC

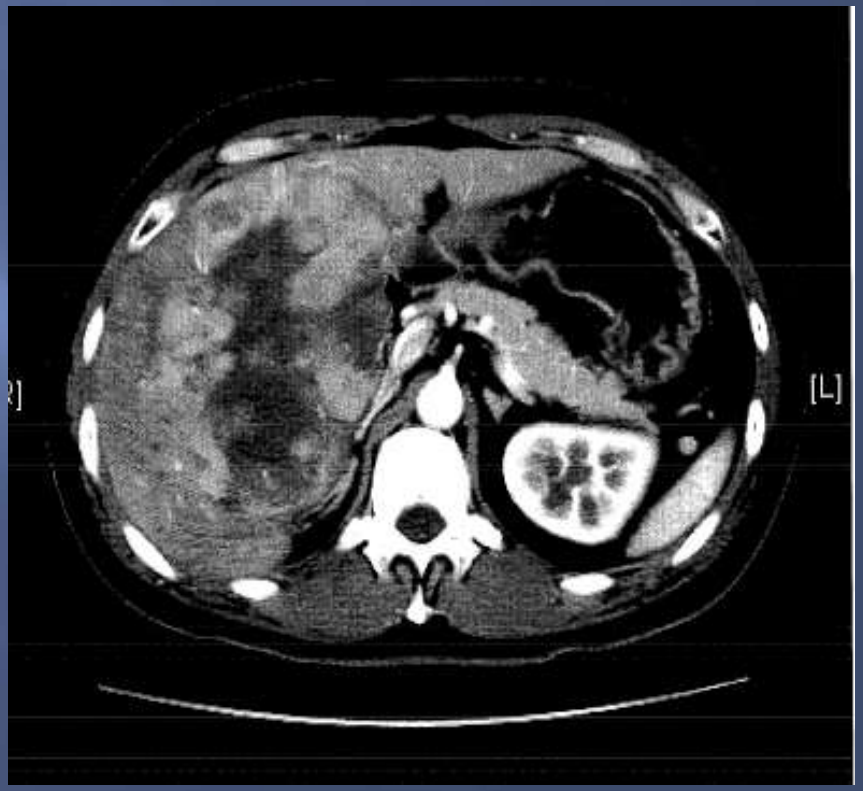
Optimizing SIRT for HCC

Three clinical scenarios on SIRT use

- Large Tumor
- Portal vein thrombosis
- Elderly population
- HK treatment algorithm

Case 1

- M/47; HBsAg +ve
- Epigastric distension
- Bulky HCC in S5/6, max diameter 16cm; no PVT
- Child's A cirrhosis
- Inoperable disease



BCLC intermediate stage HCC

- Intra-hepatic disease (without extra-hepatic metastases)
- Multifocal disease vs. Large tumor
- No vascular invasion
- Standard treatment: TACE

For this patient

- TACE for large disease
  - Young patient; aims for aggressive treatment (rather than palliative treatment)
  - Radiologic response rate is likely low

Table 3 | Rate of initial compact lipiodolisation relating tumour multiplicity and size

Variables	Values	*P*-value
Multiplicity		
Single	68/202 (33.7)	<0.001
Multiple	42/288 (14.6)	
Size in single HCC		
2–3 cm	29/63 (46.0)	<0.001
3–5 cm	33/70 (47.1)	
5–10 cm	6/44 (13.6)	
>10 cm	0/25 (0)	
Size in multiple HCC		
<3 cm	24/98 (24.5)	0.004
3–5 cm	14/66 (21.2)	
5–10 cm	4/63 (6.3)	
>10 cm	0/61 (0)	

HCC, hepatocellular carcinoma.

Values within parenthesis are expressed in percentage.

Significant response is virtually impossible in large HCC (>10cm)

Kim DY et al. AP & T 2012

SIRT-Y90

Table 2. Assessment of Radiological Response in 76 of All 108 Patients After Radioembolization with Y-90 Microspheres According to Different Criteria/Guidelines at Different Follow-up Times

	n (%)		
Radiological Response	30 Days After Treatment (n=76)	60 Days After Treatment (n=62)	90 Days After Treatment (n=62)
RECIST			
Complete or partial response	2 (3)	6 (10)	10 (16)
Stable disease	69 (90)	50 (80)	46 (74)
Progressive disease	5 (7)	6 (10)	6 (10)
RECIST including necrosis			
Complete response*	3 (4)	4 (6)	4 (6)
Partial response†	20 (26)	22 (35)	22 (35)
Stable disease	48 (63)	30 (48)	30 (48)
Progressive disease	5 (7)	6 (10)	6 (10)
WHO			
Complete or partial response	1 (1)	5 (8)	9 (15)
Stable disease	70 (92)	50 (80)	49 (79)
Progressive disease	5 (7)	7 (11)	4 (6)
WHO including necrosis			
Complete response‡	3 (4)	5 (8)	2 (3)
Partial response§	19 (25)	18 (29)	23 (37)
Stable disease	49 (64)	32 (52)	33 (53)
Progressive disease	5 (7)	7 (11)	4 (6)

Patient population
- >50% target volume: 39%
- BCLC stage C: 51%

Modified RECIST
- CR=6%; PR =35%

RECIST: Overall size: 16% had PR

Hilgard et al. Hepatology 2010

SIRT-Y90 vs. TACE

- Shorter time to achieve partial response
  - EASL criteria: 1.2 vs. 2.2 months, p=0.016

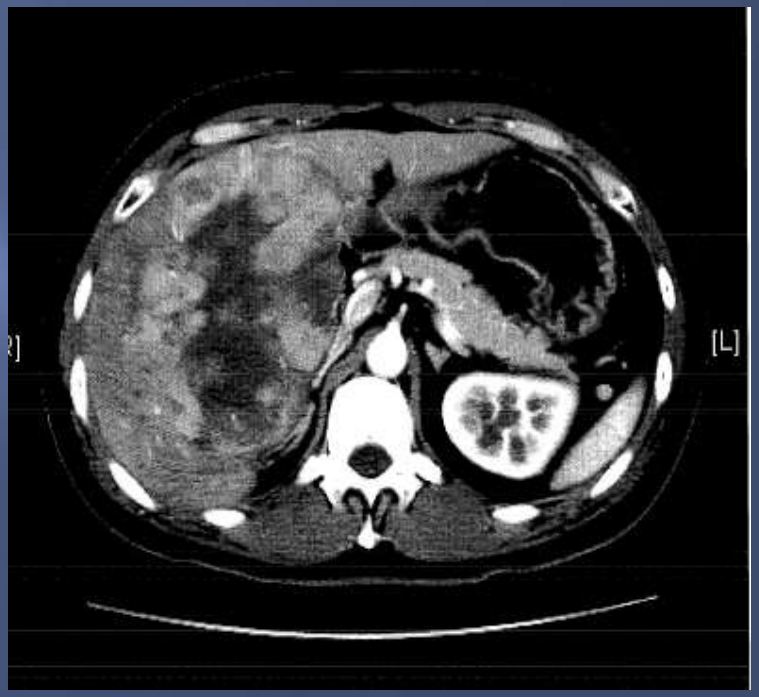
Table 3. Imaging and Survival Outcomes

Characteristic	TACE n = 122	^{90}Y n = 123	*P* value	Adjusted *P* value[a]	TACE n = 122	^{90}Y n = 123	*P* value	Adjusted *P* value[a]
		WHO response				EASL response		
Time to response (mo) (95% CI)	10.3 (7.7–16)	6.6 (4.2–8.6)	.025	.050	2.2 (1.5-3.0)	1.2 (1.1-2.1)	.008	.016
Overall response rate	44/122 (36)	60/123 (49)	.052	.104	84/122 (69)	88/123 (72)	.748	
Child–Pugh A								
Overall	25/67 (37)	36/67 (54)	.082	.164	43/67 (64)	52/67 (78)	.128	
T1/T2	7/24 (29)	12/22 (55)	.134		20/24 (83)	19/22 (86)	1.00	
T3	9/18 (50)	15/24 (63)	.533		12/18 (67)	21/24 (88)	.139	
T4a (≥4 tumors)	9/25 (36)	9/21 (43)	.764		11/25 (44)	12/21 (57)	.554	

Salem R et al. Gastroenterology 2011

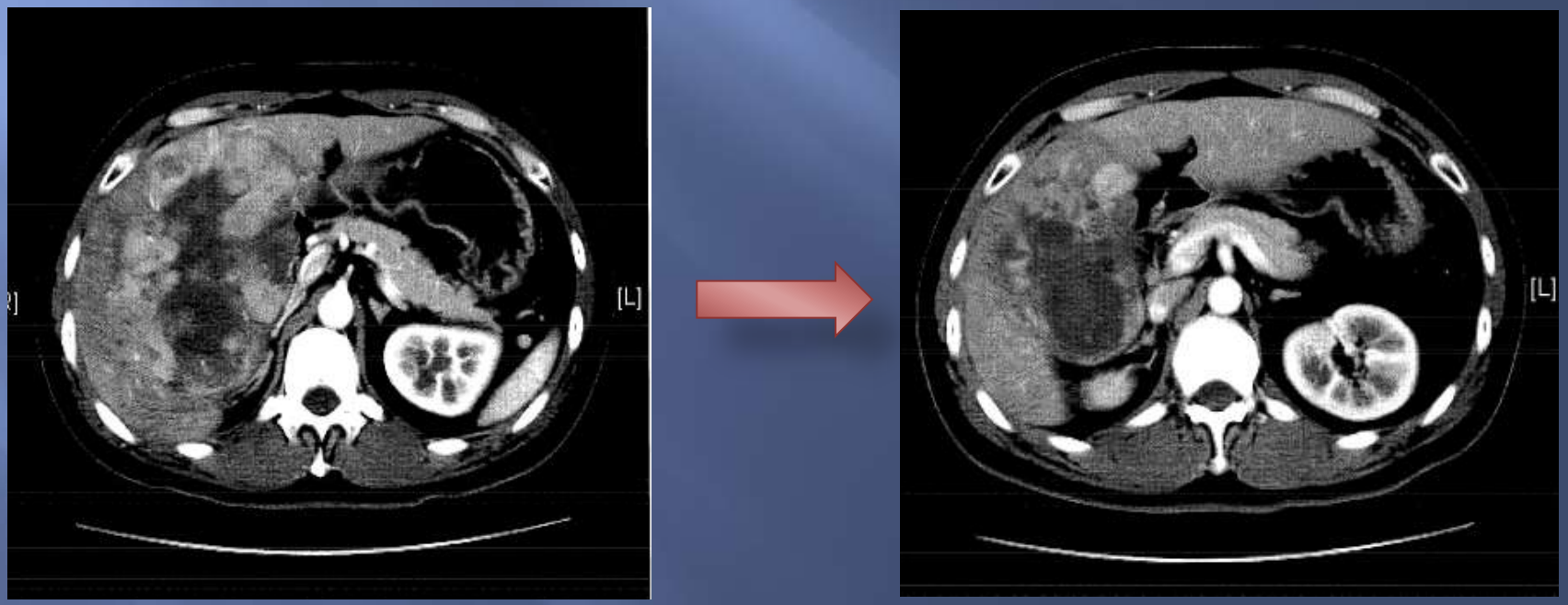
Case 1: Progress

- Joint Multidisciplinary decision:
  - Y90 resins 3Gbq (Mar 2012)



Case 1: Progress

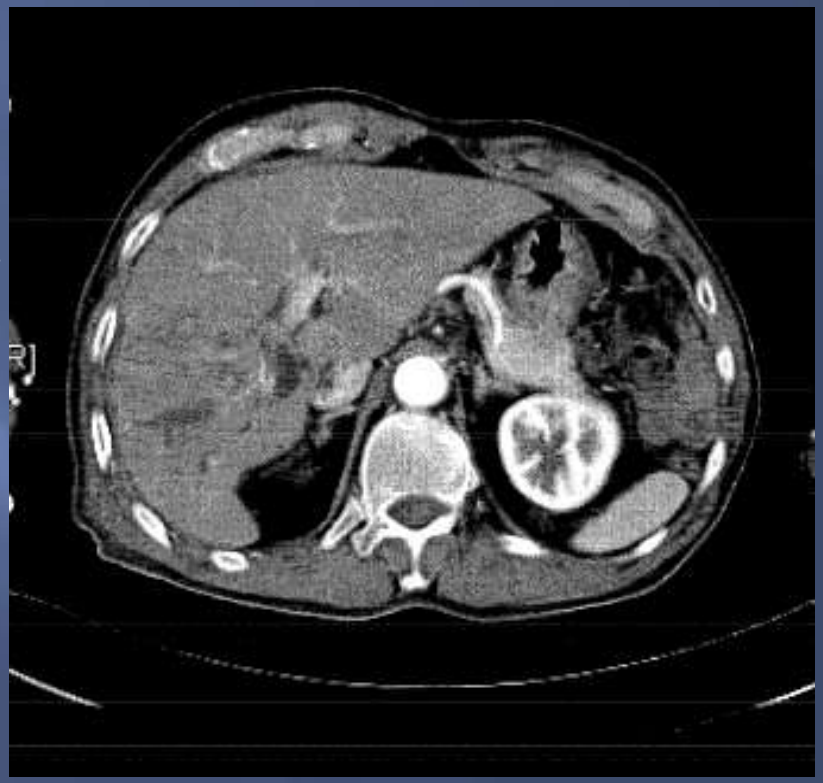
- Progress: Reduction in size of right lobed tumor
- Portal vein embolization and right hepatectomy in July 2012
- Survive at last follow-up in Oct 2013



Downstaging after 4 month

Case 2

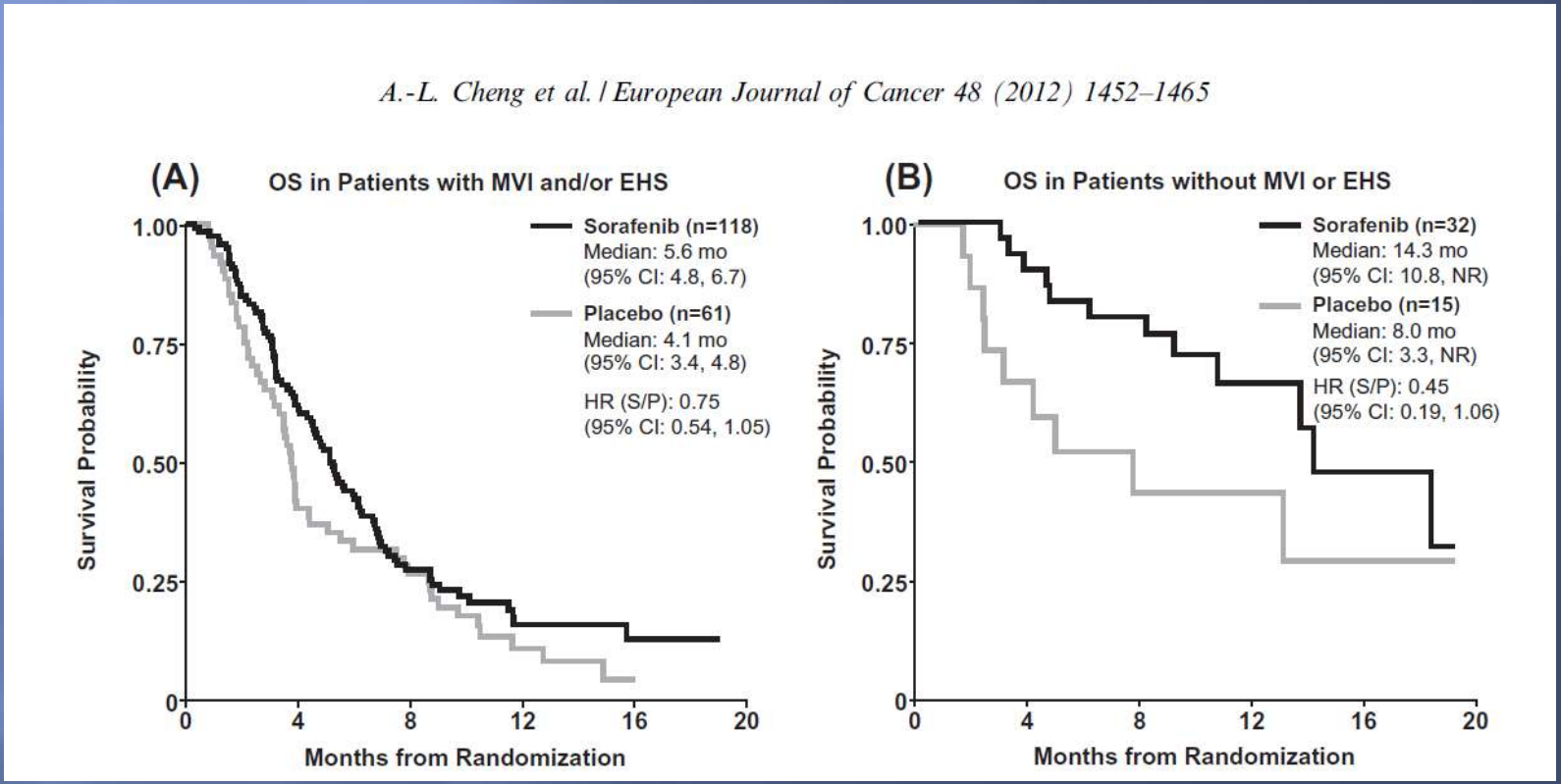
- M/60, HBsAg +ve
- AFP >2000 ng/ml
- HCC with portal vein invasion



Portal vein thrombosis/invasion

- One of the poorest prognostic factor
- Associated with complications (e.g. variceal bleeding)
- Contraindicated to TACE
- Treatment standard: sorafenib

SIRT in patients with PVT



Cheng AL et al. Eur J Cancer. 2012

SIRT in patients with PVT

Table 1. Summary of Large Series Reporting On Long-Term Outcome After ^{90}Y Radioembolization

		Intermediate Stage		Branch PVT		Main PVT		Branch or Main PVT	
Reference	Child-Pugh	N	OS* (95% CI)	N	OS (95% CI)	N	OS (95% CI)	N	OS (95% CI)
Hilgard et al.[27] (N = 108)	A/B	51	16.4 (12.1-NC)					33	10 (6-NC)
Salem et al.[3] (N = 291)	A	48	17.3 (13.7-32.5)	19	16.6 (8.8-24)	16	7.7 (3.3-13.2)	35	10.4 (7.2-16.6)
	B	35	13.5 (6.4-25.4)	27	6.5 (5-8.5)	30	4.5 (2.9-6.6)	57	5.6 (4.5-6.7)
Sangro et al.[7] (N = 325)†	A	82	18.4 (13.6-23.2)	44	10.7 (8.3-17.1)	32	9.7 (4.8-11.8)	76	10.2 (7.7-11.8)
	B	5	3.6 (2.4-10.8)						
Mazzaferro et al.[33] (N = 51)	A	15	18 (13-38)	23	17 (13-21)	5	9 (4-NC)		
	B	2	–	6	8 (5-10)	1	5		

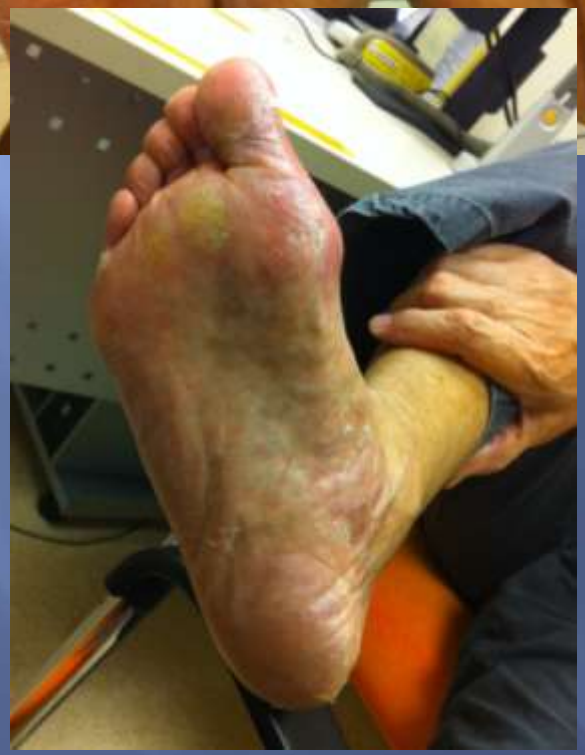
95% CI, 95% confidence interval; NC, not calculable.

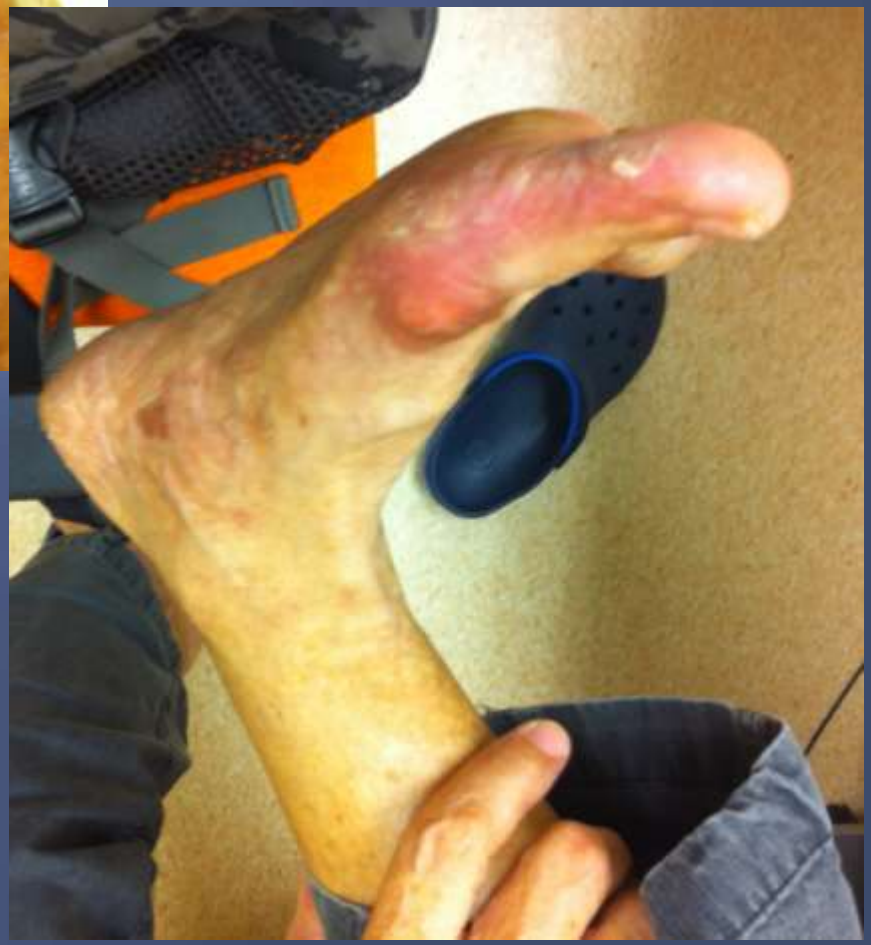
*Months.

†Unpublished data for branch and main PVT cohorts provided by authors.

Salem…Sangro . Hepatology 2013

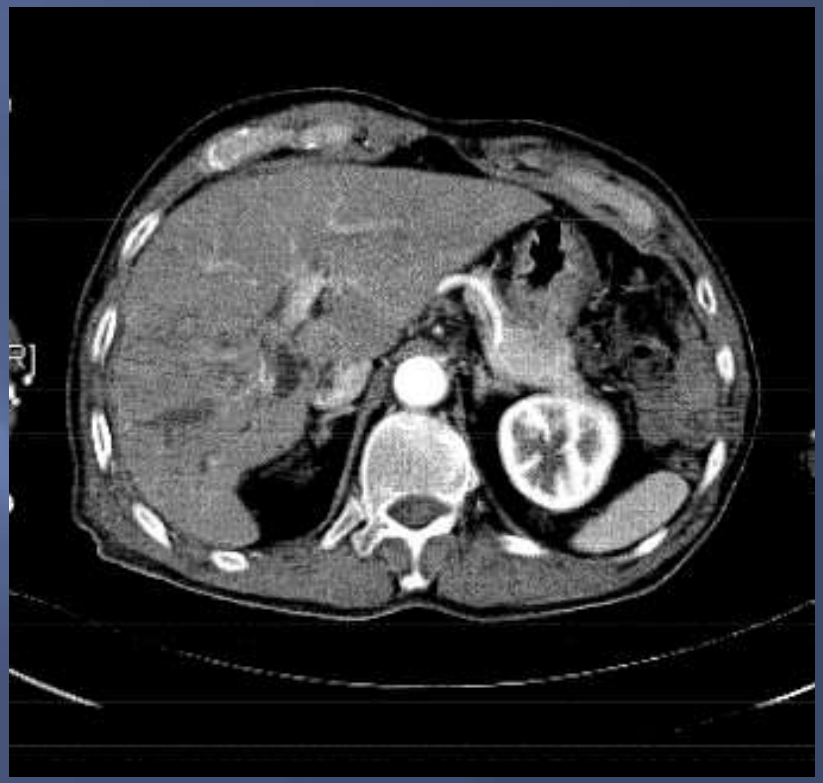
Hand foot skin reaction of sorafenib



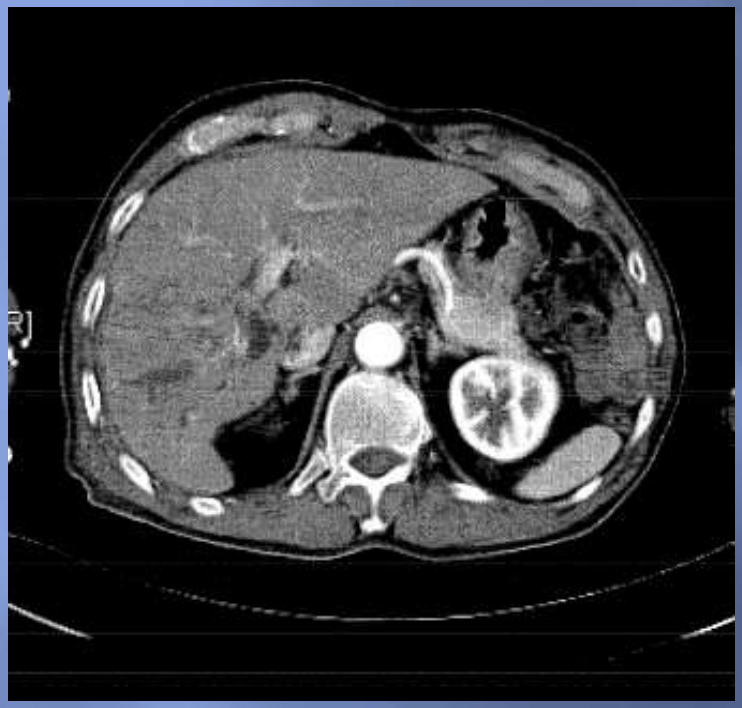


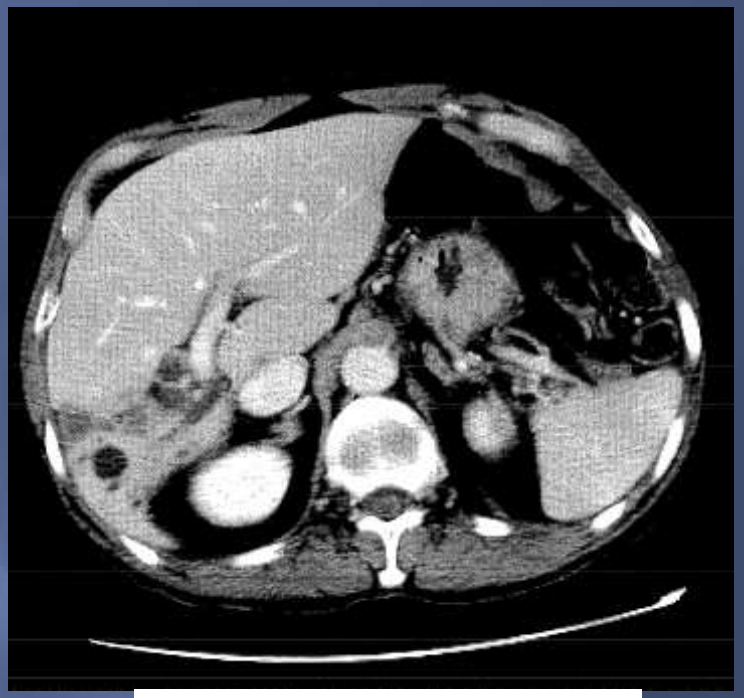
Case 2

- M/60, HBsAg +ve
- AFP >2000 ng/ml
- HCC with portal vein invasion
- Y90 SIR (2 GBq) June 2012



Case 2: Progress



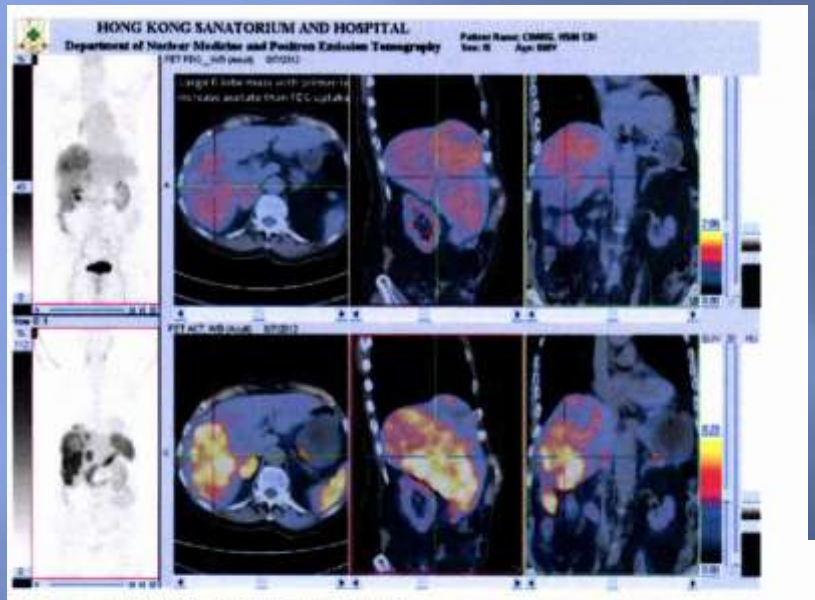


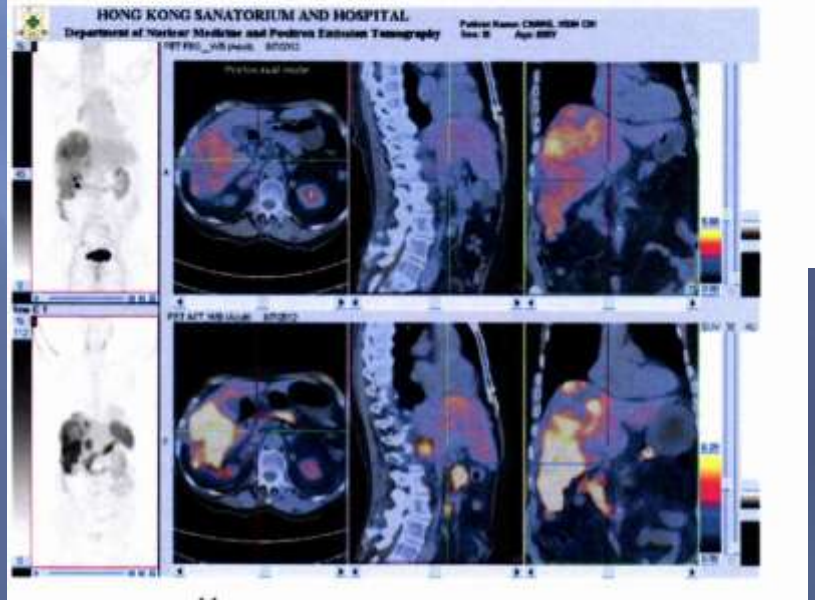
- Improving trend of portal vein thrombosis
- Last Follow-up in Sept 2013, remained SD

SIRT →

	Serum AFP < 7 ug/l
Jan 16 2012	1133 *
Feb 16 2012	1628 *
Apr 15 2012	2354 *
Apr 16 2012	2077 *
May 2 2012	2374 *
May 21 2012	2910 *
May 29 2012	2505 *
Jun 26 2012	2553 *
Jul 18 2012	212 *
Sep 12 2012	4

Case 3





Patient with inoperable and metastatic HCC
M/88
ECOG 0
HBV carrier
Pre Treatment AFP 304,500ngml

Functional parameters of these lesions are tabulated as below:

Chang, Hsin Chi	in mm		C-11 ACT	C-11 ACT	F-18 FDG
Site	LD	PD	SUVmax	Delayed	SUVmax
R lobe of liver mass	200.7	113.4	13.4	12.3	4.5
Segment VIII	119.3	79.6	9.1	9.5	6.3
R adrenal mass	53.0	34.8	10.1	9.7	4.3
Portocaval node	14.0	9.7	3.8	3.0	2.9

Note: LD=longest diameter; PD=diameter perpendicular to LD

Courtesy Slide of Dr. Thomas Leung

Elderly is underrepresented in phase III clinical trials on sorafenib/TACE

Phase III trial TACE vs. Control

Table 1. Baseline Characteristics of the Study Patients According to the Treatment Group

	Chemoembolization (N = 40)	Control (N = 39)
Age (yr)*	62 (53-69)	63 (53-70)
Sex (men/women)	36/4	34/5

	Embolisation (n=37)	Chemoembolisation (n=40)	Control (n=35)
Demography			
Age, years*	64 (62–67)	63 (61–66)	66 (64–68)
M/F	30 (81%)/ 7 (19%)	32 (80%)/ 8 (20%)	23 (66%)/ 12 (34%)

Phase III trial Sorafenib vs. Control

	Sorafenib group (n=150)	Placebo group (n=76)
Median age, years (range)	51 (23–86)	52 (25–79)
Male, n (%)	127 (84·7)	66 (86·8)

Table 1. Demographic and Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Variable	Sorafenib (N=299)	Placebo (N=303)
Age — yr	64.9±11.2	66.3±10.2

Toxicity of SIRT in elderly

No statistically significant difference in clinical toxicity between elderly and young population

Table 2. Main procedure-related clinical adverse events in the elderly (≥70 years) and younger patients (<70 years) in the first 3 months post-treatment by severity (CTCAE v3).

CTCAE Study sub-group	N	CTCAE v3: number (%) of patients						*p* value between sub-groups†
		All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Fatigue								
Age ≥70 yr	128	68 (53.1%)	58 (45.3%)	8 (6.3%)	2 (1.6%)	0	0	0.658
Age <70 yr	197	109 (55.3%)	94 (47.7%)	9 (4.6%)	6 (3.0%)	0	0	
Nausea and/or vomiting								
Age ≥70 yr	128	41 (32.0%)	36 (28.1%)	5 (3.9%)	0	0	0	0.806
Age <70 yr	197	63 (32.0%)	53 (26.9%)	9 (4.6%)	1 (0.5%)	0	0	
Abdominal pain								
Age ≥70 yr	128	31 (24.2%)	26 (20.3%)	5 (3.9%)	0	0	0	0.165
Age <70 yr	197	57 (28.9%)	44 (22.3%)	8 (4.1%)	5 (2.5%)	0	0	
Fever								
Age ≥70 yr	128	19 (14.8%)	17 (13.3%)	2 (1.6%)	0	0	0	0.269
Age <70 yr	197	21 (10.7%)	19 (9.6%)	2 (1.0%)	0	0	0	
GI ulceration								
Age ≥70 yr	128	3 (2.3%)	0	2 (1.6%)	1 (0.8%)	0	0	0.320
Age <70 yr	197	9 (4.6%)	3 (1.5%)	1 (0.5%)	4 (2.0%)	0	1 (0.7%)	

CTCAE v3: Common Terminology Criteria for Adverse Events version 3.0.
†*p* Value for CTCAE distribution comparison between cohorts by Cochran-Mantel-Haenszel row mean score test statistic.

Golfieri et al. J Hepatol 2013; 59:753-61

Toxicity of SIRT in elderly

Higher risk of hypoalbuminemia and elevation of ALT

Table 3. Comparison of laboratory toxicities in the elderly (≥70 years) and younger patients (<70 years) by severity (CTCAE v3) between baseline and month 3.

CTCAE Study sub-group	N	Pre-radioembolization		Month 3		Change of CTCAE grade at month 3			*p* value between sub-groups†
		All grades	Grade ≥3‡	All grades	Grade ≥3‡	Decreased	Same	Increased	
Total bilirubin									
Age ≥70 yr	117	20.5%	0	50.4%	4.3%	2.6%	59.0%	38.5%	0.432
Age <70 yr	175	24.0%	0	47.4%	6.9%	6.3%	59.4%	34.3%	
Albumin									
Age ≥70 yr	97	38.1%	0	45.4%	1.0%	10.3%	62.9%	26.8%	0.018
Age <70 yr	140	37.9%	0	35.7%	0.7%	13.6%	72.9%	13.6%	
ALT									
Age ≥70 yr	109	53.2%	1.8%	57.8%	2.8%	11.0%	67.9%	21.1%	0.015
Age <70 yr	163	63.8%	1.8%	57.1%	3.7%	18.4%	70.6%	11.0%	
INR									
Age ≥70 yr	113	23.0%	0	33.6%	0	3.5%	82.3%	14.2%	0.911
Age <70 yr	164	22.0%	0	29.9%	3.0%	4.3%	80.5%	15.2%	
Creatinine									
Age ≥70 yr	115	8.7%	0	13.0%	0	2.6%	89.6%	7.8%	0.906
Age <70 yr	161	8.1%	0.6%	10.6%	2.5%	1.2%	91.9%	6.8%	
Platelets									
Age ≥70 yr	102	47.1%	1.0%	52.0%	1.0%	9.8%	74.5%	15.7%	0.408
Age <70 yr	166	42.8%	3.0%	53.0%	4.8%	9.0%	71.1%	19.9%	

Golfieri et al. J Hepatol 2013; 59:753-61

Survival of elderly treated with SIRT

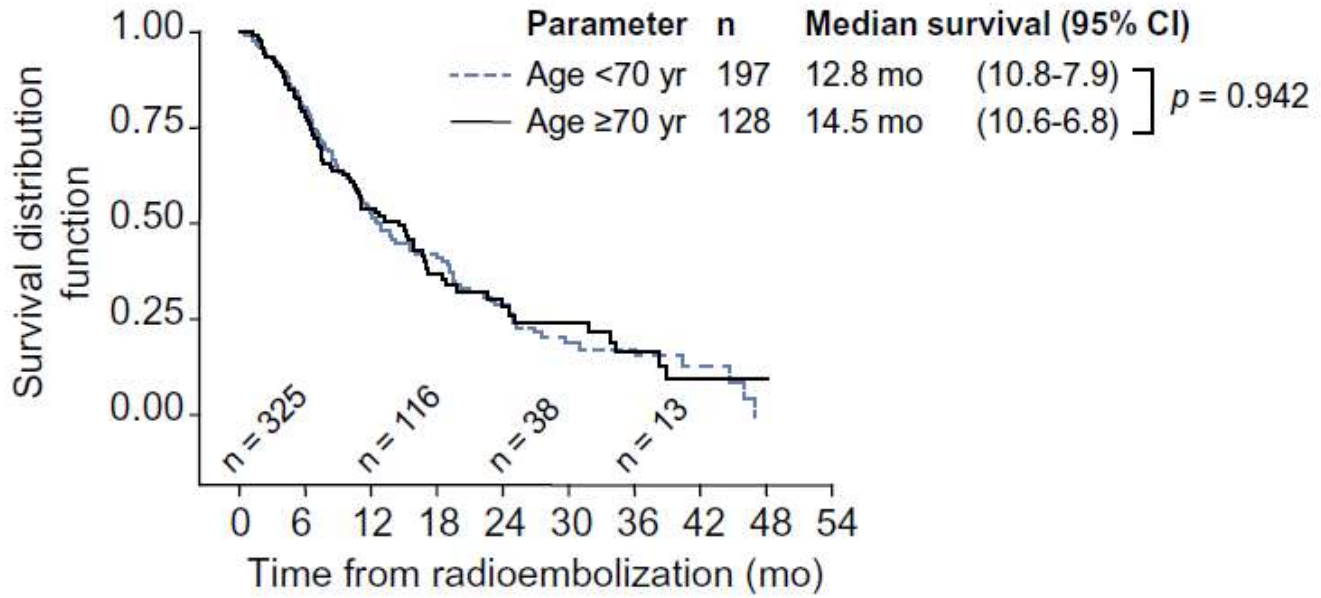
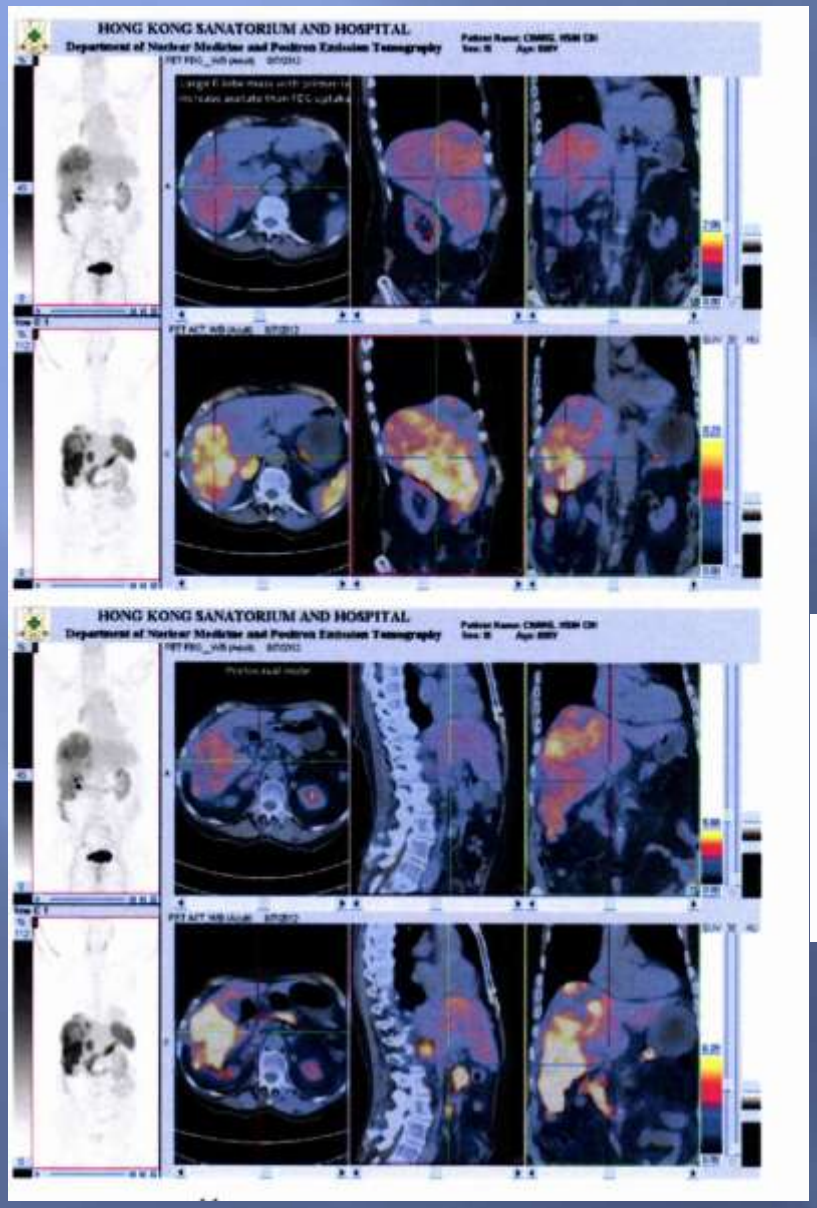


Fig. 1. Kaplan-Meier analysis of overall survival by age.

Golfieri et al. J Hepatol 2013; 59:753-61

Case 3



Patient with inoperable HCC
M/88
HBV carrier
Pre Treatment AFP 304,500ngml

Received 2.5 GBq Y90 on 28 August 2012
Tolerated treatment well

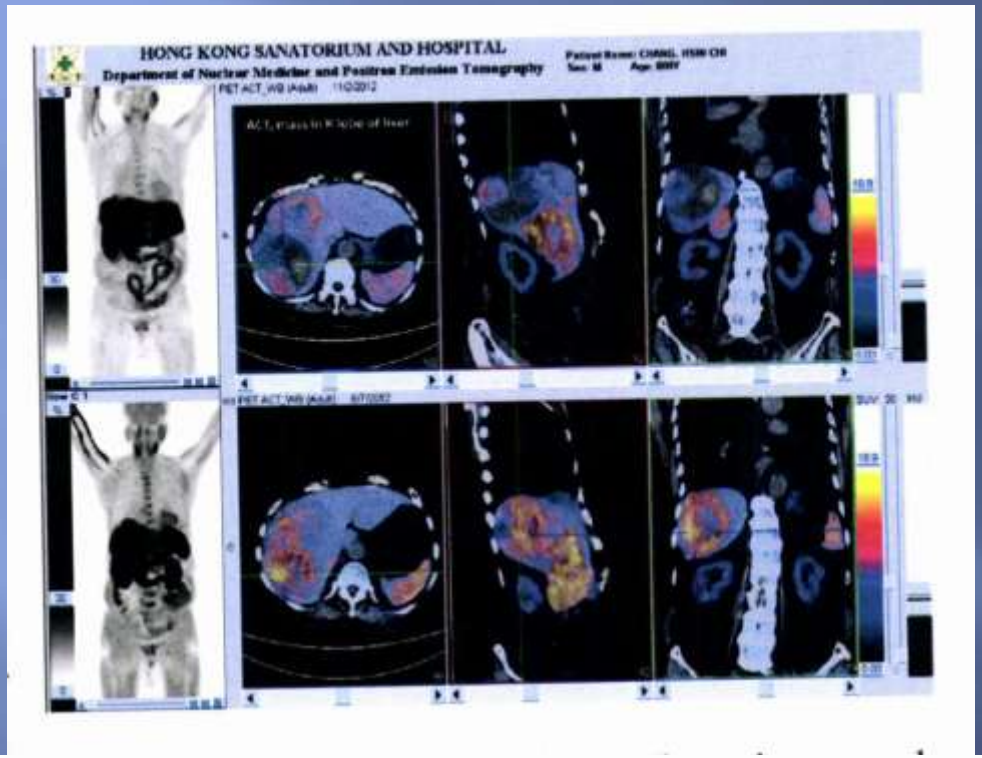
Functional parameters of these lesions are tabulated as below:

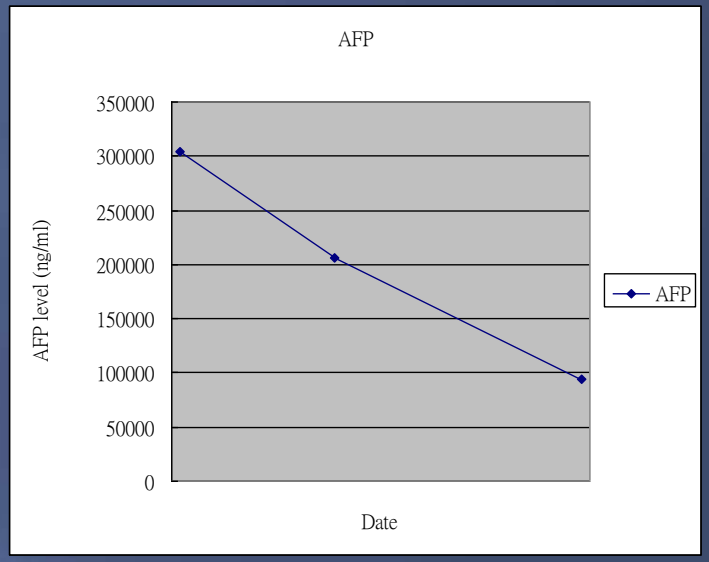
Chang, Hsin Chi	in mm		C-11 ACT	C-11 ACT	F-18 FDG
Site	LD	PD	SUVmax	Delayed	SUVmax
R lobe of liver mass	200.7	113.4	13.4	12.3	4.5
Segment VIII	119.3	79.6	9.1	9.5	6.3
R adrenal mass	53.0	34.8	10.1	9.7	4.3
Portocaval node	14.0	9.7	3.8	3.0	2.9

Note: LD=longest diameter; PD=diameter perpendicular to LD

Courtesy Slide of Dr. Thomas Leung

Post treatment: PET scan and AFP trend





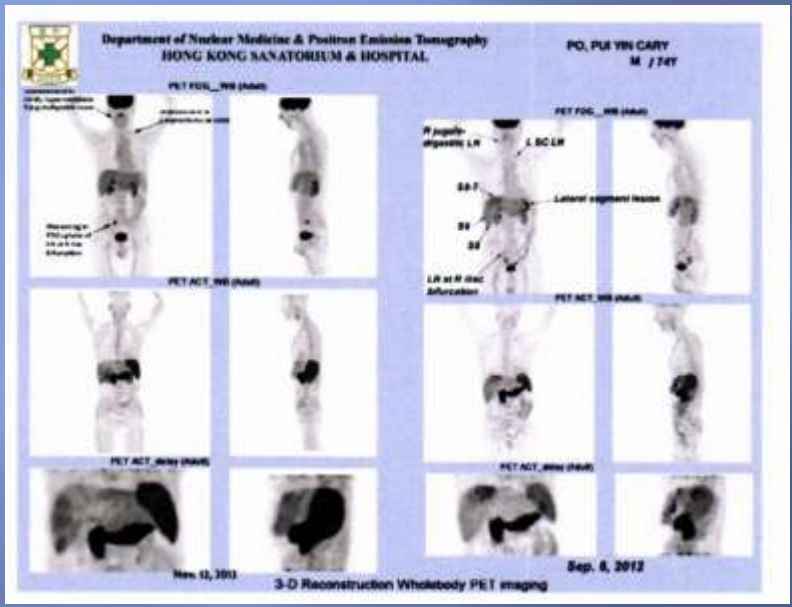
Functional parameters to compare these 2 studies are tabulated below:

	11/2/2012					8/7/2012					
Chang, Hsin Chi	in mm					in mm					
Site	LD	PD	C11	F-18 FDG	TLG	LD	PD	C11	F-18 FDG	FDG TLG	TLG% change
R lobe of liver mass	97.4	85.4	9.9	3.5	370.0	200.7	113.4	13.4	4.5	4888.2	-92.4%
Segment VIII	106.4	78.1	11.9	4.7	855.9	119.3	79.6	9.1	6.3	1463.6	-41.5%
R adrenal mass	72.0	41.5	8.0	3.7	190.3	53.0	34.8	10.1	4.3	113.6	67.6%
Portocaval node	14.2	9.2	7.0	1.8	0.5	14.0	9.7	3.8	2.9	0.7	-28.6%

Note: LD=longest diameter; PD=diameter perpendicular to LD; TLG=total lesion glycolysis (vol x SUVmean)

Courtesy Slide of Dr. Thomas Leung

Post treatment: PET scan

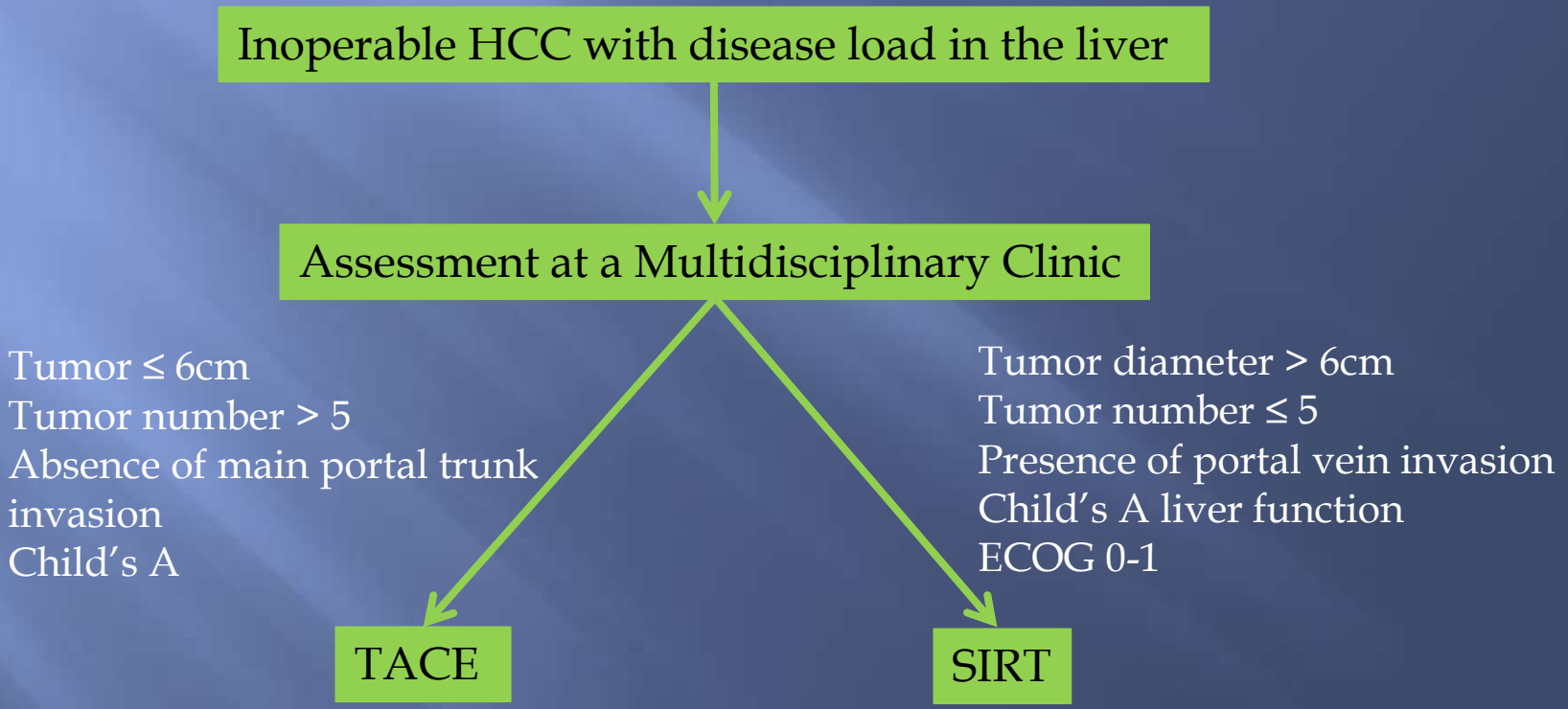


Impression:

1. Dual-radiopharmaceutical PET evaluation demonstrates normalized of ^{18}FDG uptake and near normalized ^{11}C-acetate uptake in virtually all the bilobar liver tumors with no significantly increased uptake in the hypodense liver lesions. The findings are suggestive of bilobar liver tumors rendered metabolic quiescent.

Courtesy Slide of Dr. Thomas Leung

Treatment for inoperable intrahepatic HCC at Prince of Wales Hospital, Hong Kong



Avoid use of SIRT in following settings

- Bilirubin level > 2 ULN
- Uncontrolled ascites
- Extensive or aggressive disease in extra-hepatic organs
- Patients with compromised lung reserves (e.g. COAD with frequent exacerbation)

Optimization of SIRT use for HCC

- Close collaboration between clinical management team and nuclear medicine
  - Reasonable report time
  - Accurate volumetric assessment
  - Needs communication +/- learning curve

LUNG

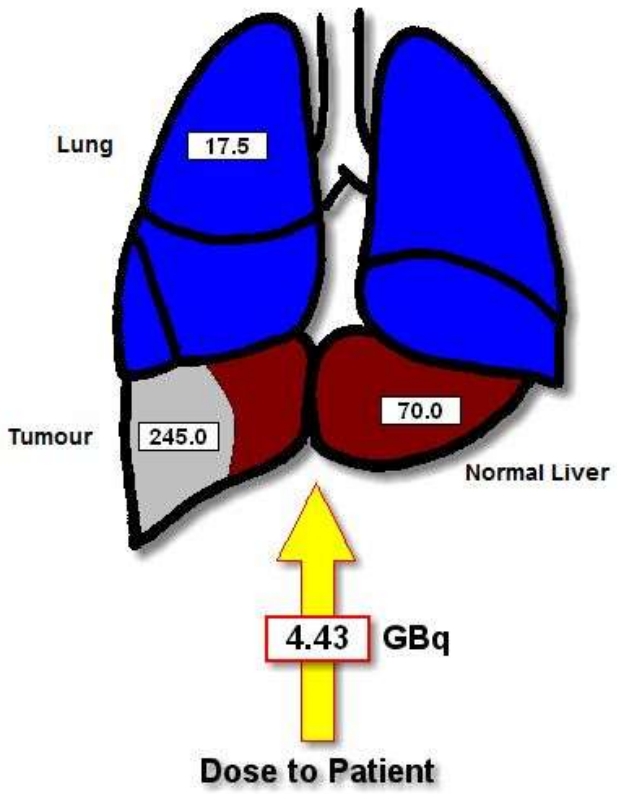
dose limit:	20	Gy *
volume:	1.000	liter
^{99m}Tc-MAA:	25.0	MBq
lung-shunting:	8.2	%
allowed dose:	5.06	GBq
prescribed dose:	4.43	GBq
resulting dose:	17.5	Gy *

NORMAL LIVER

dose limit:	70	Gy *
volume:	1.400	liter
^{99m}Tc-MAA:	140.0	MBq
T/N-ratio:	3.50	
allowed dose:	4.43	GBq
prescribed dose:	4.43	GBq
resulting dose:	70.0	Gy *

TUMOUR

max dose:	no limit	
volume:	0.400	liter
^{99m}Tc-MAA:	140.0	MBq



CT-SCAN
volume determination

whole liver:	1.8	liter
- tumour:	0.4	liter
= normal liver:	1.400	liter

^{99m}Tc-MAA-SCAN
distribution simulation

lung:	25	MBq
+ whole liver:	280	MBq
= total:	305.0	MBq
lung-shunting:	8.2	%
whole liver:	280.0	MBq
- tumour:	140	MBq
= normal liver:	140.0	MBq
T/N ratio:	3.50	

CALC EDIT RESET

**Due to the limitations of the MIRD Model the values in Gy do not reflect the true delivered dose to the particular organs.*

Conclusion

- SIRT is an effective locoregional therapy for inoperable HCC
- SIRT fulfills the unmet need in selected patients who warrants more aggressive treatment
  - Large tumor
  - Portal vein thrombosis
- Age should not be a limiting factor
- Multidisciplinary contribution and communication
  - Physician/Oncologist, nuclear medicine/physicist, interventional radiology


Thank you