

# Rhenium-188 based Radiopharmaceuticals for Treatment of Hepatoma

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# Unmet needs of hepatoma

Early diagnosis for Local therapy

**RFA**- radiofrequency ablation

expensive, painful, incomplete treatment (? !)

**PEI**- expensive, painful, incomplete treatment (often)

**TACE**- efficacy ↓

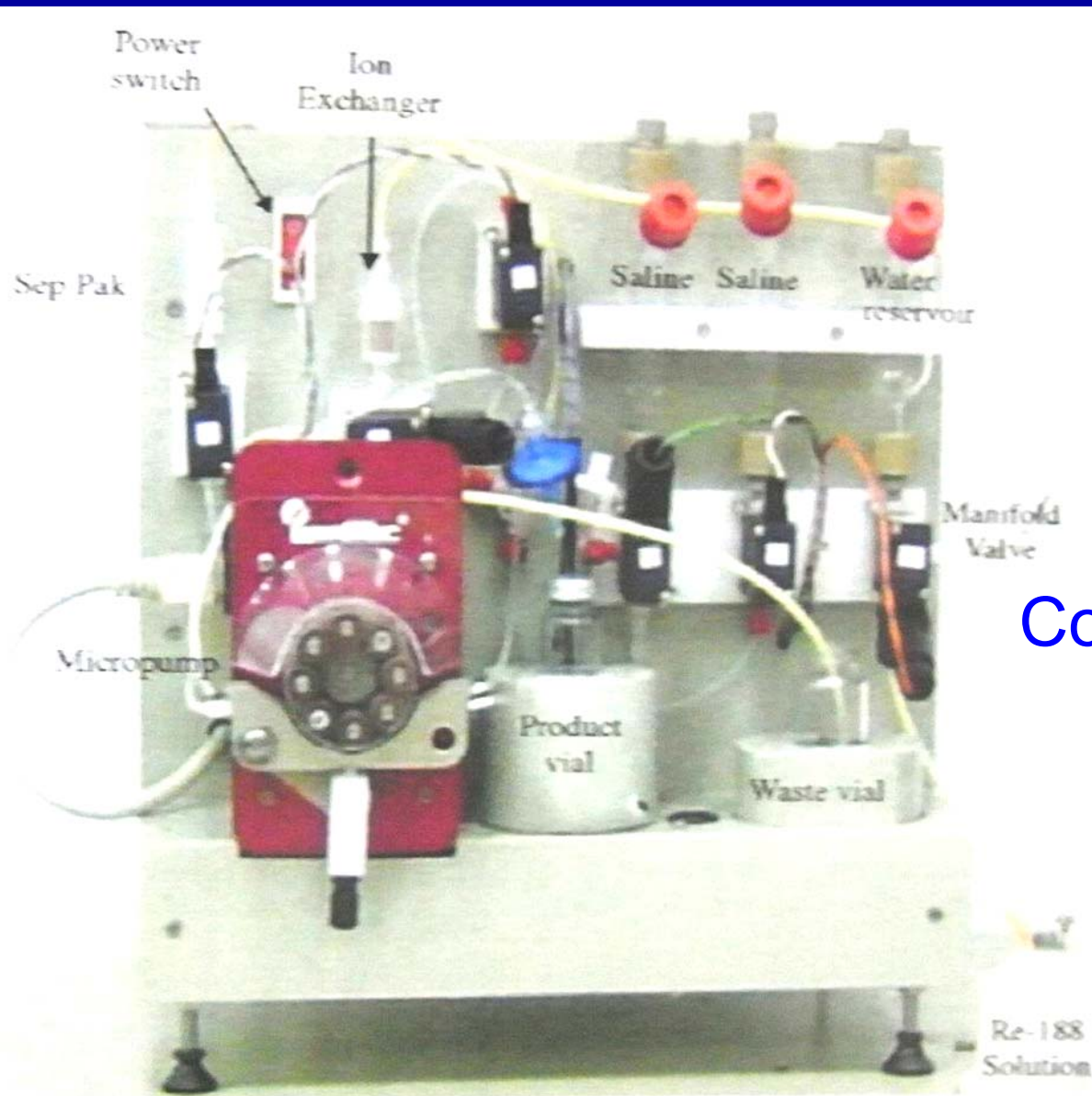
**Late stage**- vessel, bile ducts invasion.

**Metastatic tumors**- Y-90 expensive

# The superiority of Re-188

	<sup>131</sup> I	<sup>188</sup> Re	<sup>90</sup> Y
Type	β and γ	β and γ	β
β E <sub>max</sub> (MeV)	0.61	2.12	2.27
γ Energy (KeV)	364	155	
Path (Mean-range)	0.4	2.43	2.76
Half-life (hr)	193	16.9	64
10 Half-life (hrs)	1930	169	640

# Product from generator vs. reactors



Re-188 on site  
availability vs. Y-90  
importation from  
Australia or Canada

Cost of Y-90  $\doteq$  100 x Re-188

Y-90 > I-131

>>> Re-188

Re-188 estimated price  
\$1/mCi (2003)

# Rhenium 188 for clinical purposes

- Synovectomy
- Bone pain
- Other solid tumors
- Coronary artery stenosis

# $^{188}\text{Re}$ in balloon for prevention of coronary artery stenosis

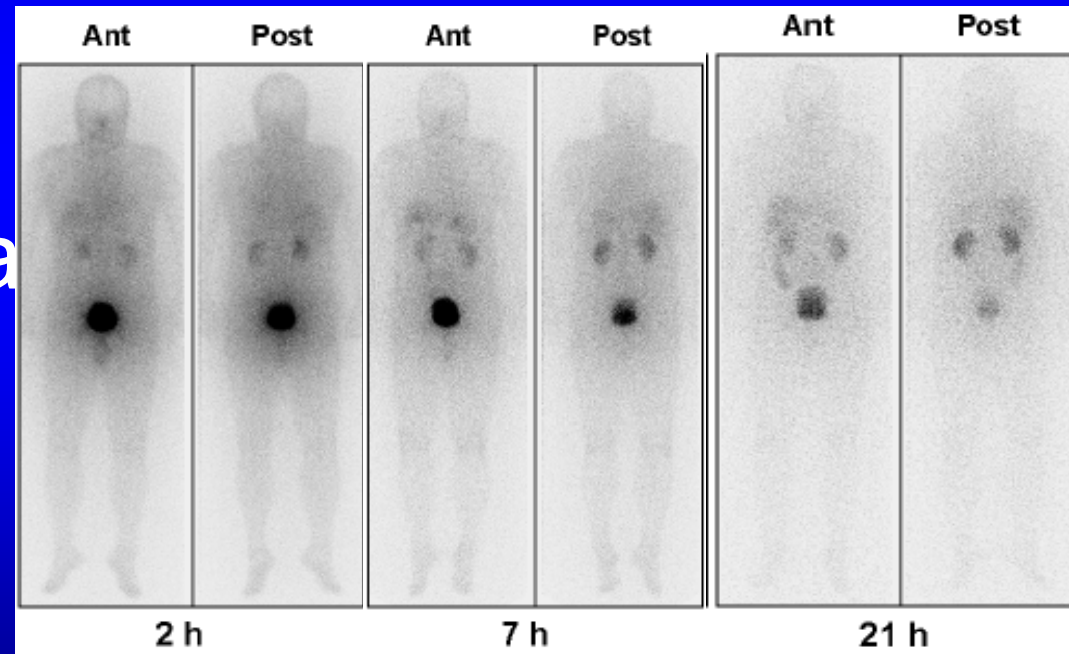
Taiwan study, the clinical trials

Safety and efficacy

Leakage—Korean data

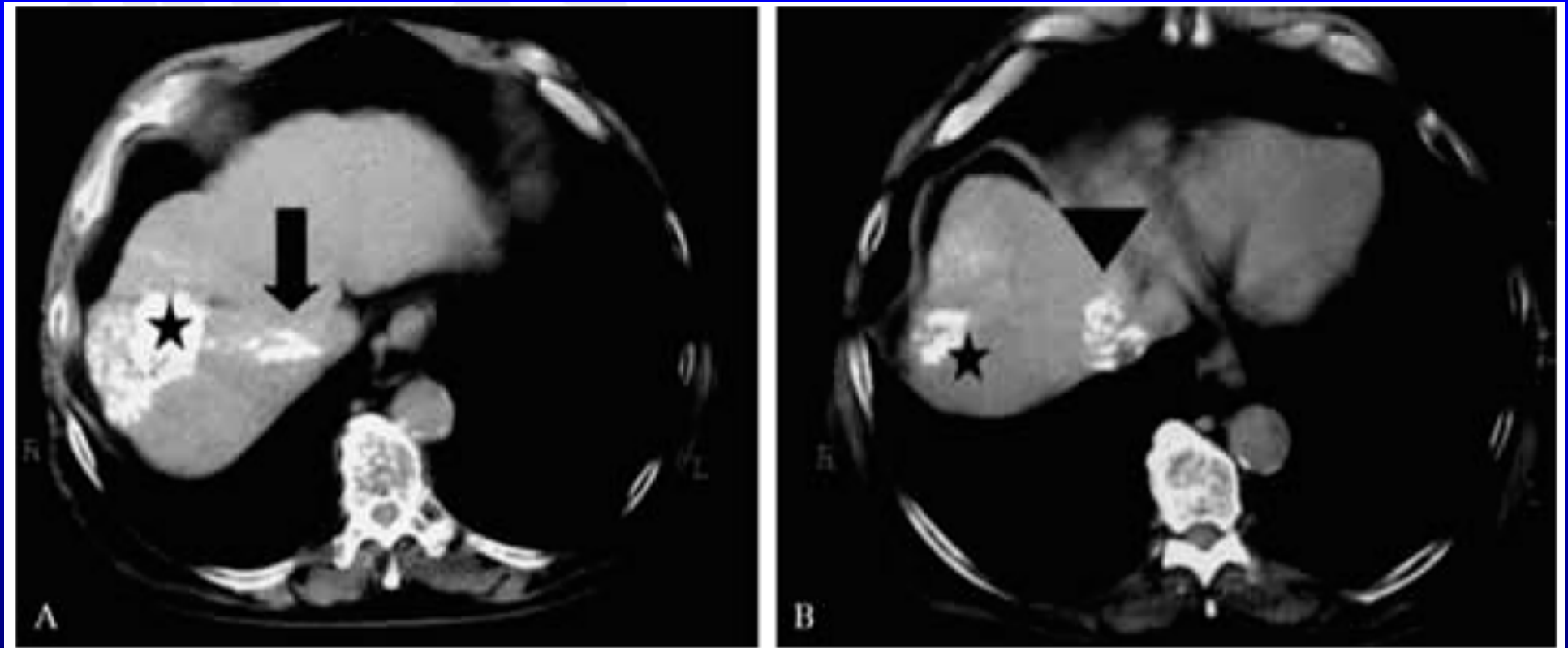
Hang CL, Ting G, et al. Chang Gung Med J 2003, Chest 2003

Paeng JC Eur J Nucl Med Mol Imaging 2003



Serial scintigraphic images after intracoronary balloon brachytherapy

Retention of Lipiodol within a hepatocellular carcinoma (star), with venous extension in the right hepatic vein (arrow) and the inferior vena cava (arrow head)



# Y-90 treatment plan

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## *Clinical exclusion criteria*

Patients **eligible for curative** resection

**Ascites** or in clinical liver failure or markedly abnormal synthetic and excretory liver function tests

Previous external beam radiation therapy to the liver

Capecitabine within the previous 2 months, or if capecitabine treatment is foreseen

uncontrolled extrahepatic metastatic disease

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# Y-90 treatment plan

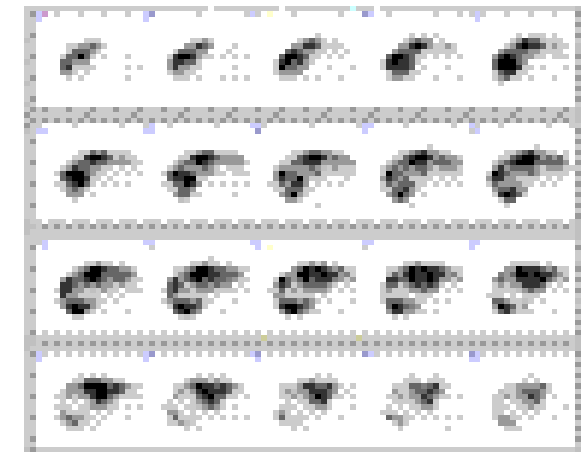
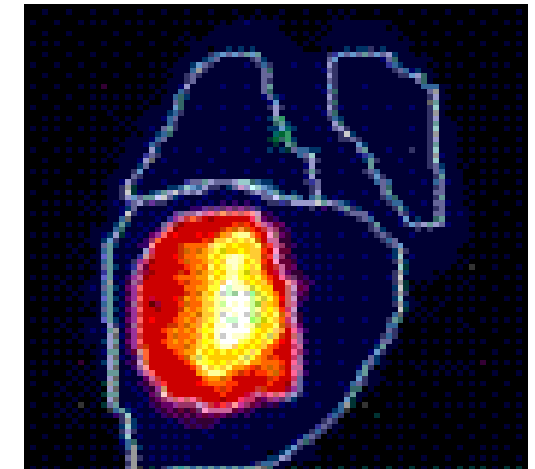
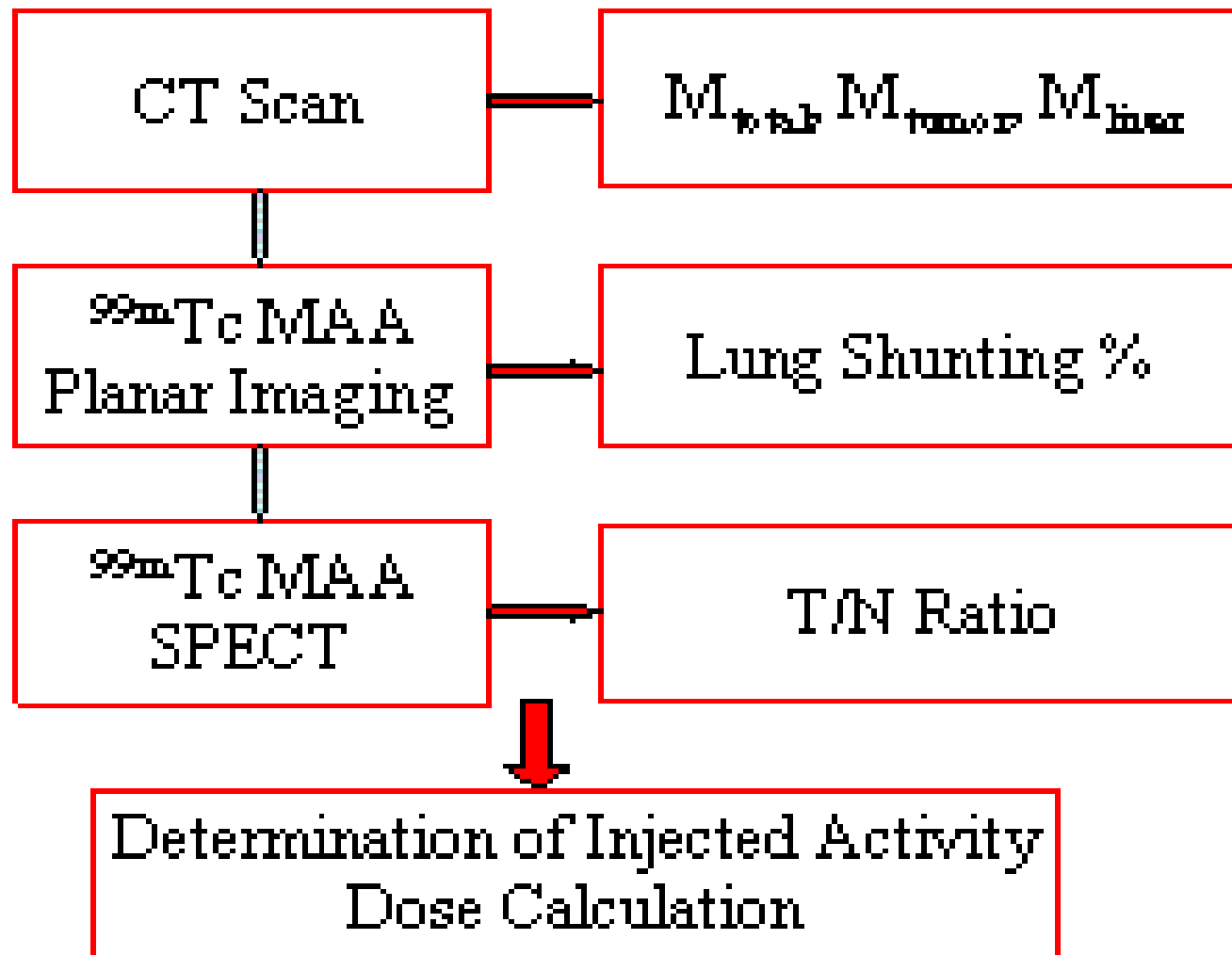
## *Imaging exclusion criteria*

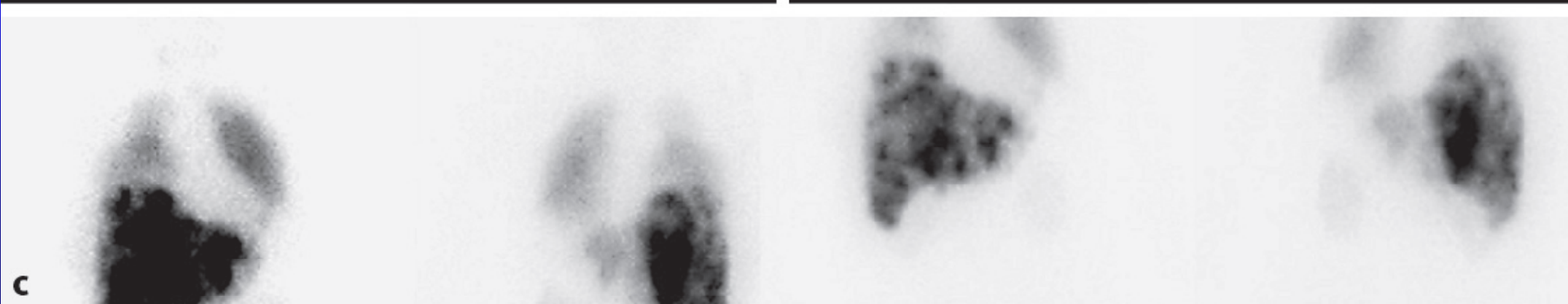
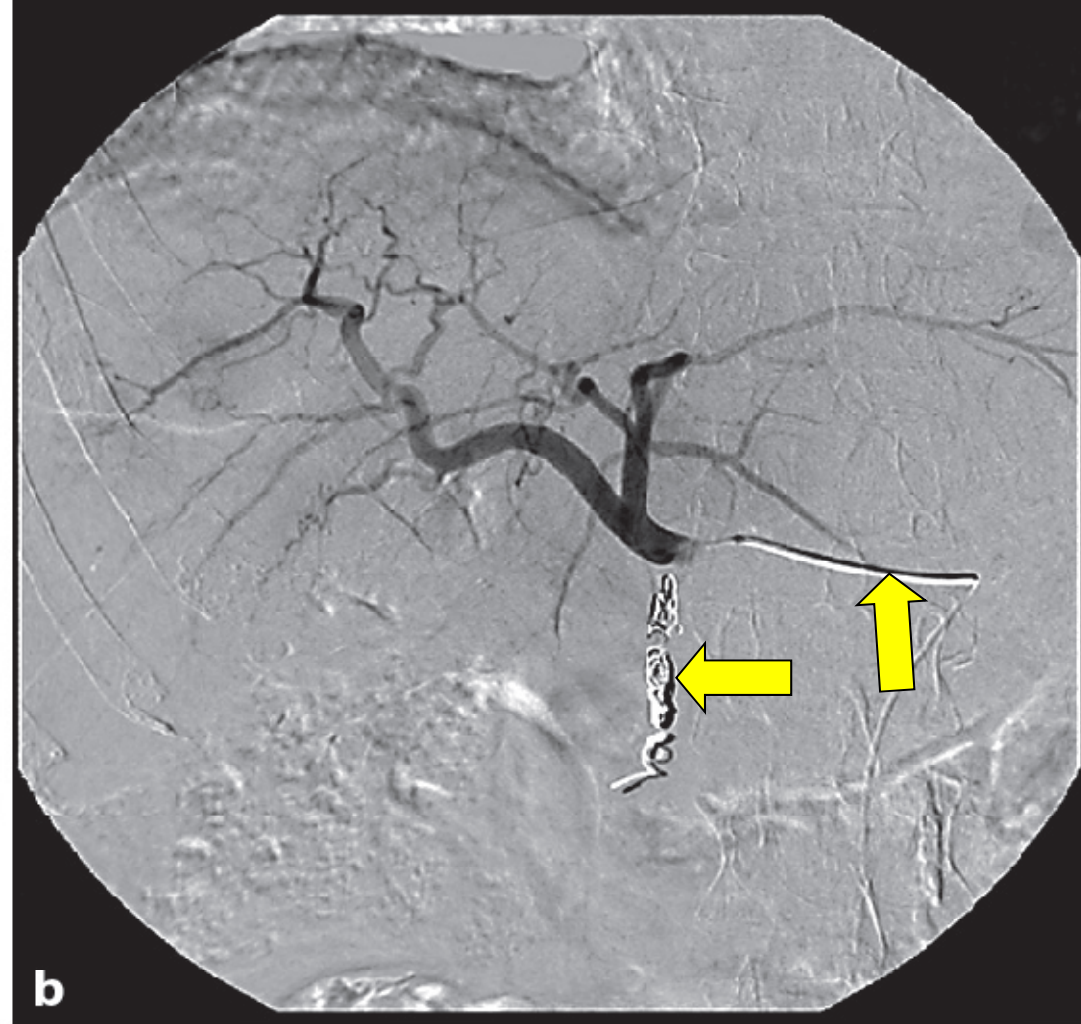
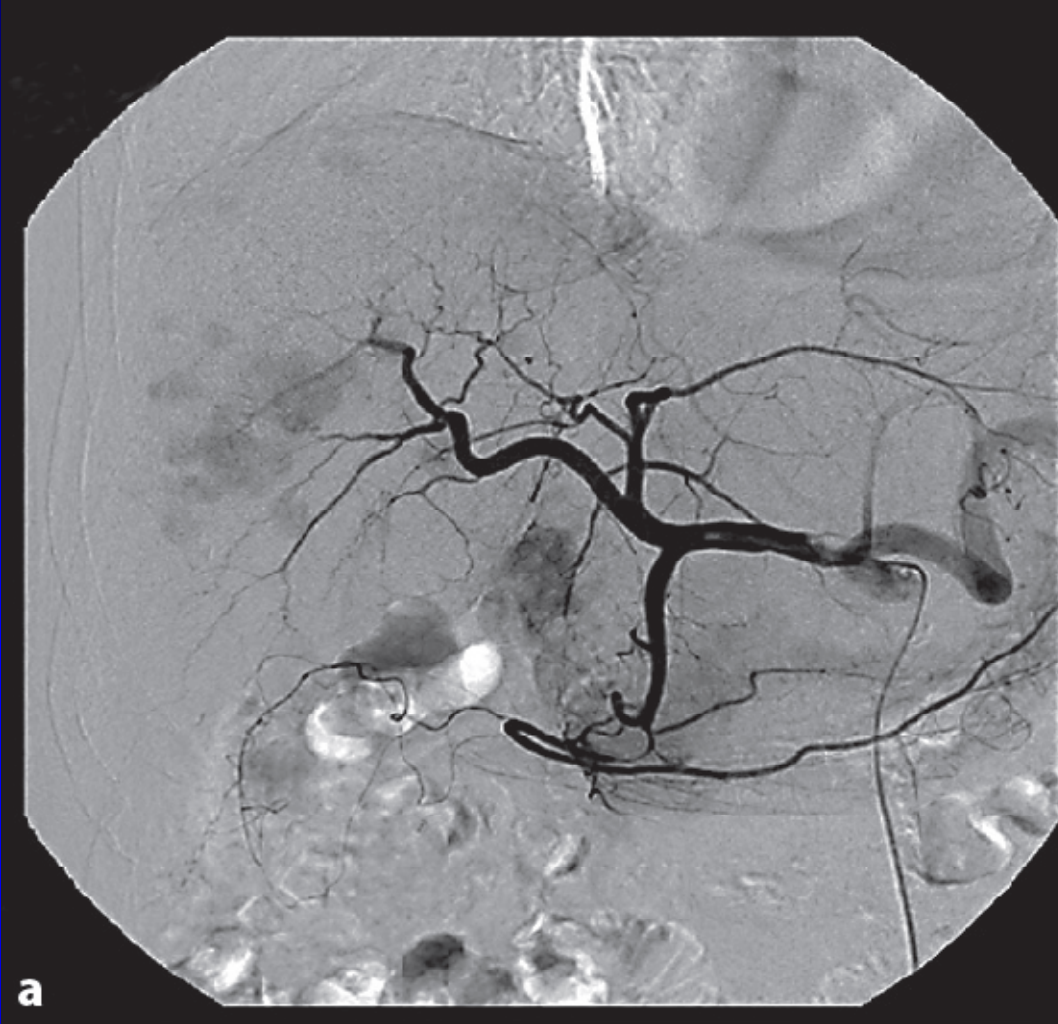
Unacceptable ( $>20\%$ ) high lung uptake on MAA-scan, if 10-20%: reduce activity

Abdominal tracer deposition outside the liver on MAA-scan (consider to repeat angiography and prophylactic embolisation procedure and  $^{99m}\text{Tc}$ -MMA injection)

(Main) Portal vein thrombosis

# Dosimetric Issues In SIRT





# Re-188 vs. Y-90

- Visible during injection at fluoroscopy
- 4F-or-5F-catheter (both)
- prophylactic embolisation of gastroduodenal arteries branching from the hepatic artery is not required with the injection of  $^{188}\text{Re}$  labelled Lipiodol.
- In over 70  $^{188}\text{Re}$ -labelled Lipiodol candidates, we had a single drop-out for anatomical reasons.
- After  $^{188}\text{Re}$  Lipiodol treatment, no distortion or destruction of the arterial supply was observed
- MAA-scan to simulate the  $^{90}\text{Y}$  application



## Dosimetric and Therapeutic Details in 93 Patients

Characteristic	Datum
Total no. of treatments	140
No. of treatments*	
1	58
2	26
3	6
4	3
RAD to organ†	
Normal liver	$0.353 \pm 0.115$
Lungs	$0.037 \pm 0.019$
Tumor	$1.491 \pm 0.519$
First administered activity of $^{188}\text{Re}$ (MBq)	$5326 \pm 1639$ (1924–10 323)
RAD to tumor(s) (cGy)	$8768 \pm 3074$ (3088–21 848)
Cumulative administered activity of $^{188}\text{Re}$ (MBq)	$7847 \pm 4756$ (1924–25 567)
Dose-limiting organ†	
Liver	75 (81)
Lungs	18 (19)

Note.—Unless otherwise specified, data are mean values  $\pm$  standard deviations, with ranges in parentheses.

\* Data are numbers of patients who underwent the given number of treatments.

† As centigrays per megabecquerel of injected activity.

‡ Data are numbers of patients, with percentages in parentheses.

## IAEA sponsored study – Rhenium 188 HDD/Lipiodol for hepatoma

### Treatment Outcome

Outcome	No. of Patients
Tumor response*	
Complete	5 (8)
Partial	17 (26)
Objective†	22 (33)
Stable disease	23 (35)
Progression	21 (32)
AFP response‡	
Complete	3 (6)
Partial	17 (31)
Objective†	20 (37)
Stable disease	18 (33)
Progression	16 (30)

Note.—Data in parentheses are percentages. Percentages may not add up to 100% owing to rounding.

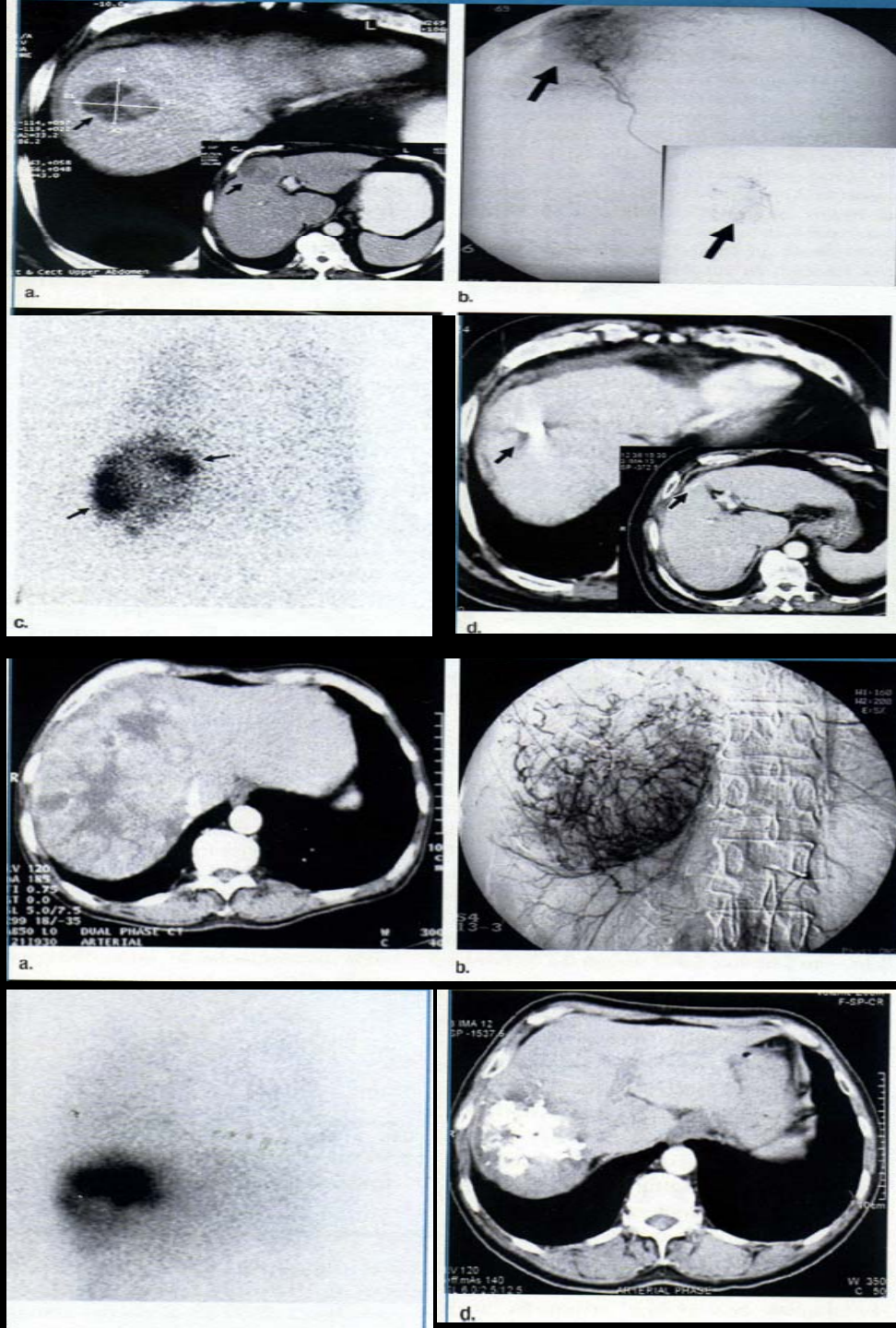
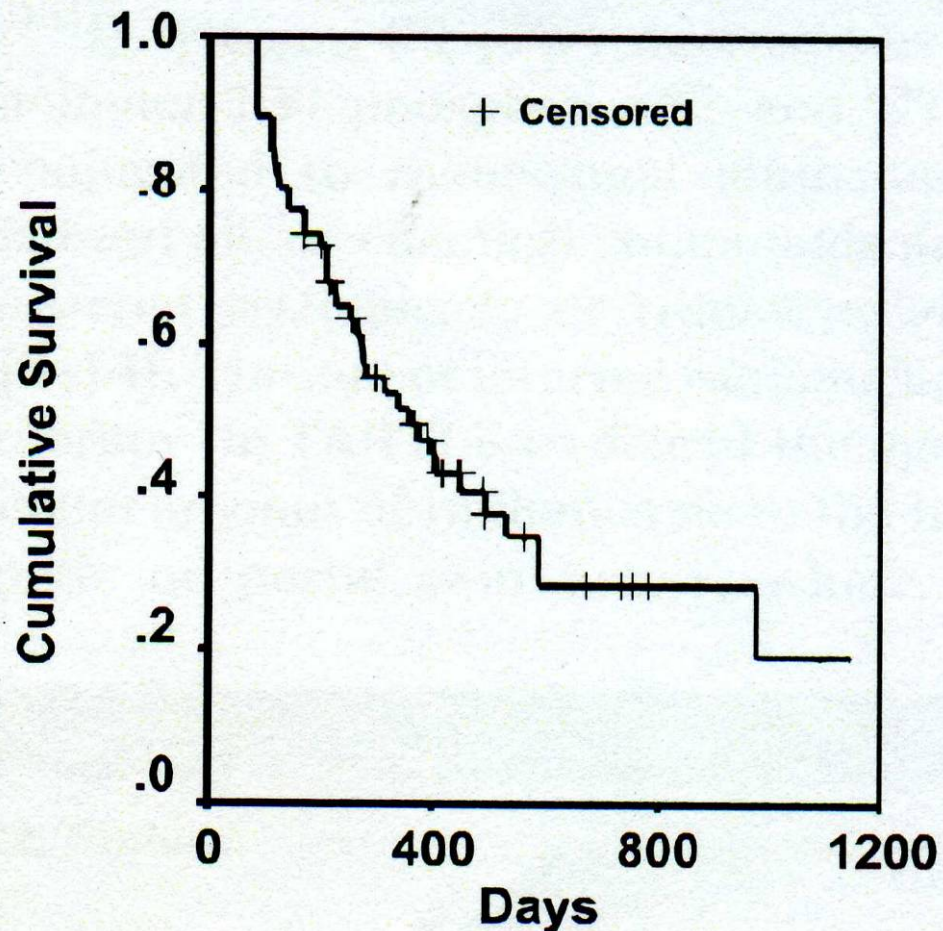
\* Data on tumor response were available for 66 patients.

† Objective response included complete and partial responses.

‡ Data on AFP response were available for 54 patients.

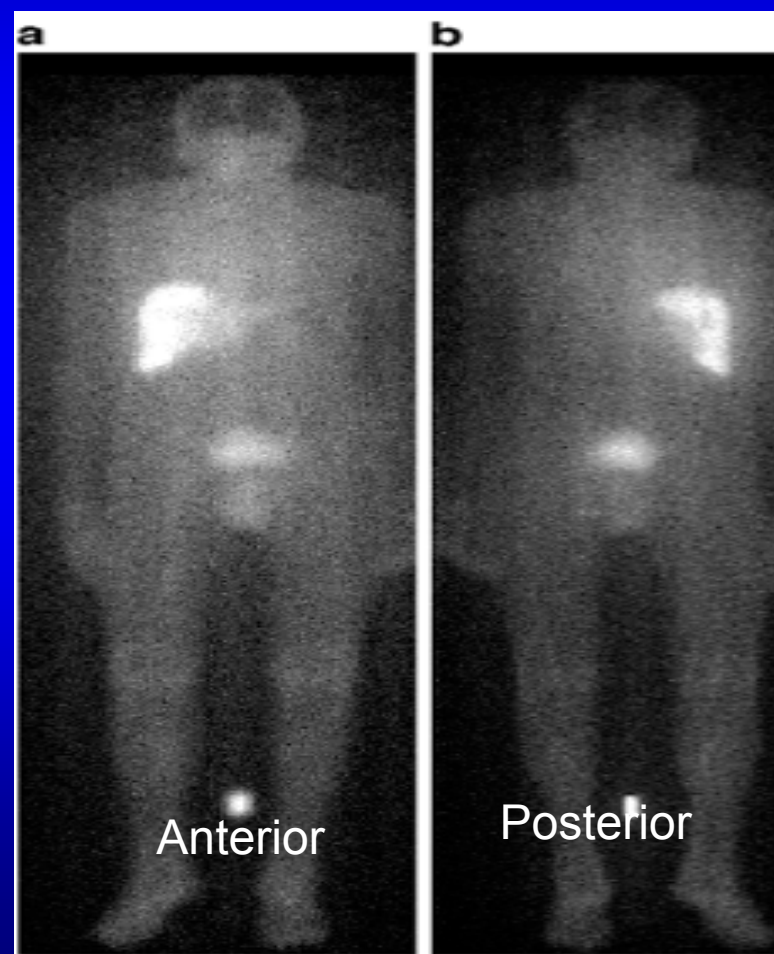


IAEA sponsored study --  
over- all survival in all  
patients (median survival  
365 days



Whole-body scintigraphy  
performed 24h 4.8GBq  $^{188}\text{Re}$ -  
HDD/lipiodol:

## Toxicity studies



	Grade 3 <i>n</i>	Grade 4 <i>n</i>
Hematologic toxicity		
WBC	2	0
Platelets	2	0
Hemoglobin	0	3
Hepatic toxicity		
AST/ALT	14	10
Bilirubin (pretreatment abN)	5 (27)	2 (6)
Digestive toxicity		
Ulcer	1	0
Diarrhea	0	1
Other toxicities		
Hypotension	1	0
pneumopathy	0	1
Clinically significant SAE	5	2

# Pharmacodynamics of Re-188 HDD/Lipiodol

	Dose range 3.7±0.2GBq	Dose range 4.6±0.3GBq	Dose range 5.8±0.3GBq	Dose range 6.8±0.2GBq
Liver including tumoral tissue	4.6-11.8	4.6-10.4	5.6-14.9	12.3-21.8
Lungs	1.7-10.4	2.0-10.3	3.8-3.9	5.6-14.7
Kidney	0.2-1.6	0.2-0.9	0.3-0.9	0.4-1.1
Whole Body	0.5-0.7	0.4-0.7	0.5-0.9	0.6-1.2



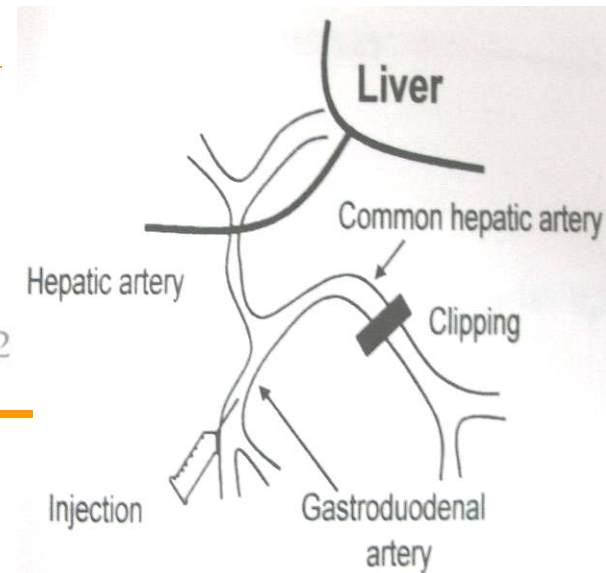
# Pharmacodynamics and pharmacokinetics of Rhenium 188 after hepatic artery injection

Organ	Time		
	1 hr	24 hr	48 hr
Blood*	$0.42 \pm 0.11^{\dagger\dagger}$	$0.09 \pm 0.04$	$0.04 \pm 0.02$
Tumor*	$11.19 \pm 4.11$	$7.30 \pm 2.20$	$3.55 \pm 1.03$
Liver*	$1.35 \pm 0.44$	$1.07 \pm 0.23$	$0.52 \pm 0.32$
Lung*	$0.80 \pm 0.50$	$0.60 \pm 0.34$	$0.52 \pm 0.34$
Spleen*	$0.13 \pm 0.06$	$0.05 \pm 0.02$	$0.07 \pm 0.04$
Muscle*	$0.06 \pm 0.03$	$0.03 \pm 0.02$	$0.02 \pm 0.01$
Bone*	$0.27 \pm 0.04$	$0.11 \pm 0.06$	$0.04 \pm 0.01$
Brain <sup>†</sup>	$0.04 \pm 0.01$	$0.003 \pm 0.0008$	$0.0009 \pm 0.0002$
Thyroid <sup>†</sup>	$1.05 \pm 0.03$	$0.05 \pm 0.03$	$0.005 \pm 0.003$
Stomach <sup>†</sup>	$0.34 \pm 0.15$	$0.13 \pm 0.03$	$0.01 \pm 0.006$
Intestine <sup>†</sup>	$0.41 \pm 0.11$	$0.05 \pm 0.02$	$0.01 \pm 0.005$
Kidney*	$4.02 \pm 1.44$	$1.25 \pm 0.46$	$0.62 \pm 0.32$
Urine <sup>†</sup>	$2.95 \pm 1.94$	$2.56 \pm 1.74$	$0.06 \pm 0.04$

\* : The number of animals in each group was eight.

<sup>†</sup> : The animal used in these organs was four.

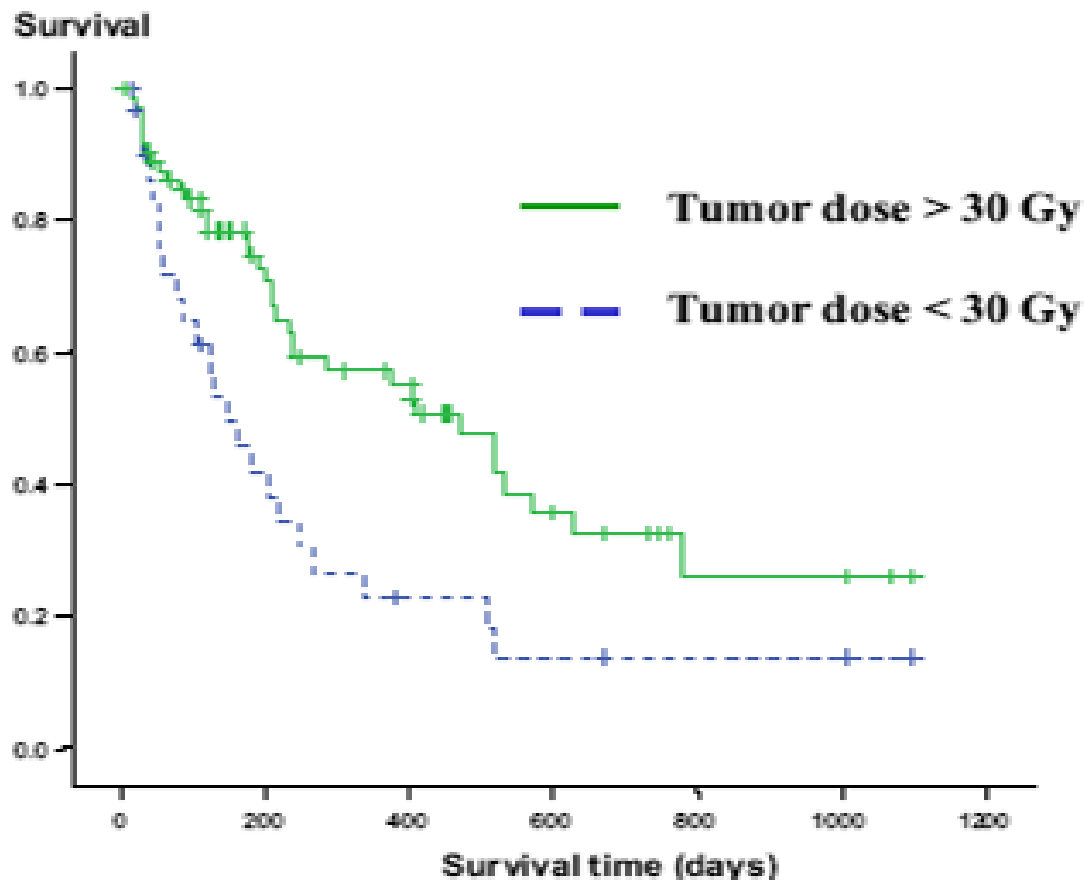
<sup>††</sup> : All the data were expressed as mean  $\pm$  SD.



# If higher tumor dose, better response, then, local treatment?

Low yield of HDD labelling

- Microsphere
- $^{188}\text{Re}$ -ECD/Lipiodol



**Figure 3** Overall survival (Kaplan-Meier method; comparison using the log-rank test) was significantly better ( $P = 0.006$ ) among patients whose tumor dose was greater than 30 Gy ( $n = 33$ ). (Color version of figure is available online.)

# Microsphere local injection of Re-188

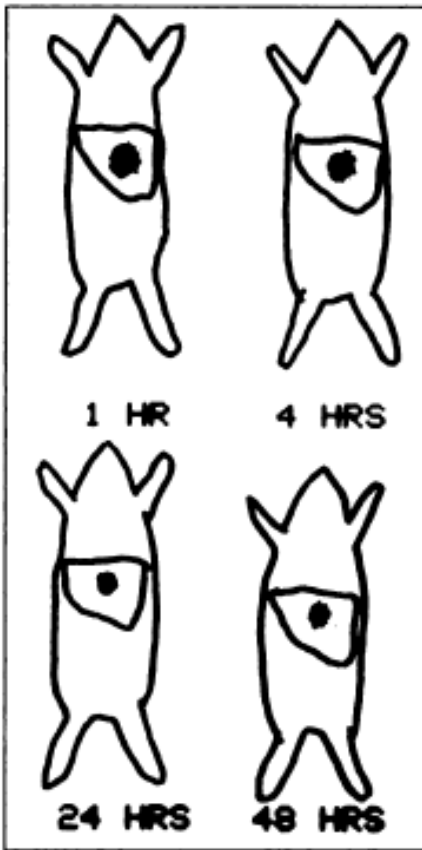
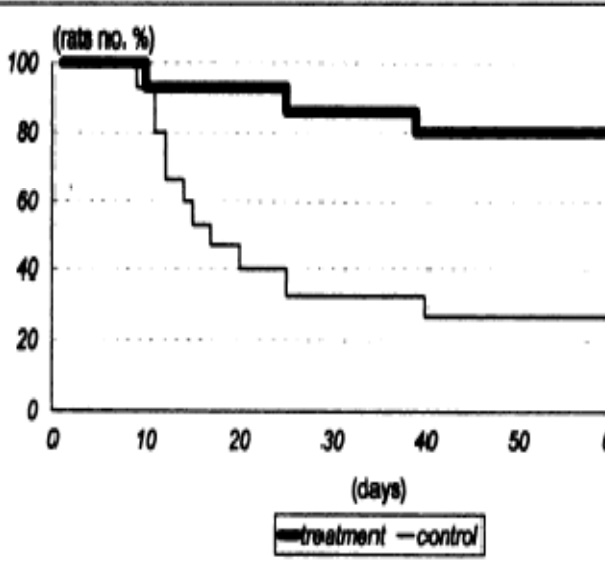
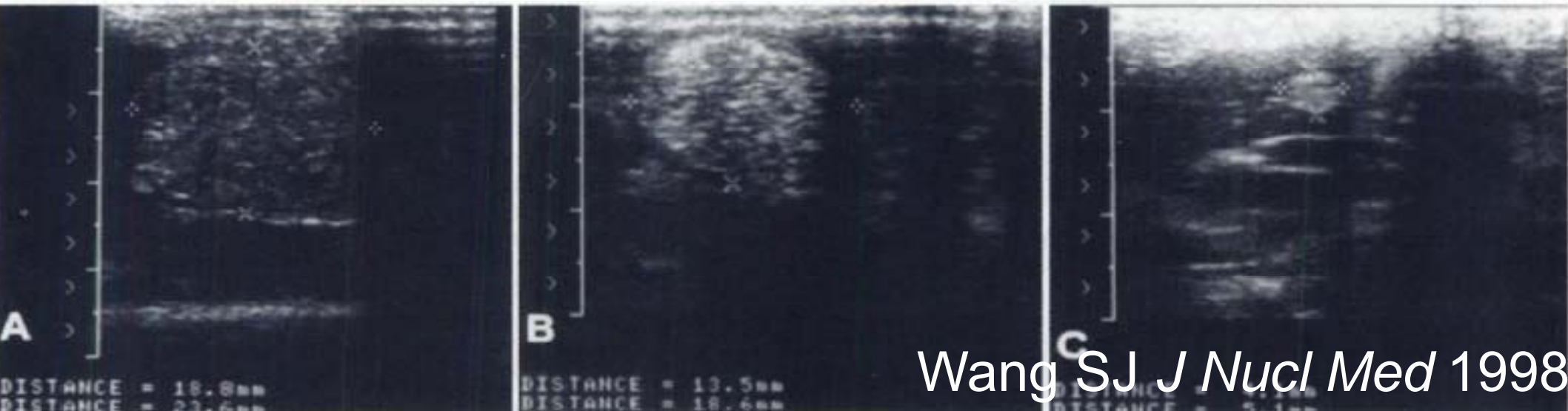


TABLE 1  
Doses (mGy) to Various Tissues in Rats with Hepatoma  
after Intratumoral Injection of Rhenium-188 Microspheres

Tissue	Dose (mGy/MBq)
Tumor*	636
Liver	1.22
Lung	0.253
Kidney	0.164
Spleen	0.019
Testis	0.0007
Muscle	0.0006
Red marrow	0.126
Bone surface	0.008
Urinary bladder wall	1.61

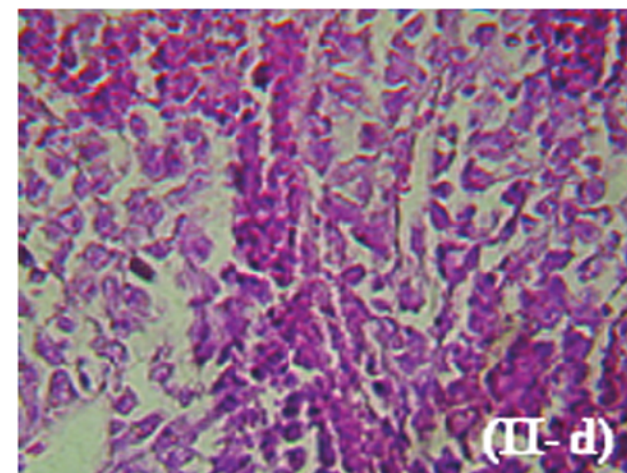
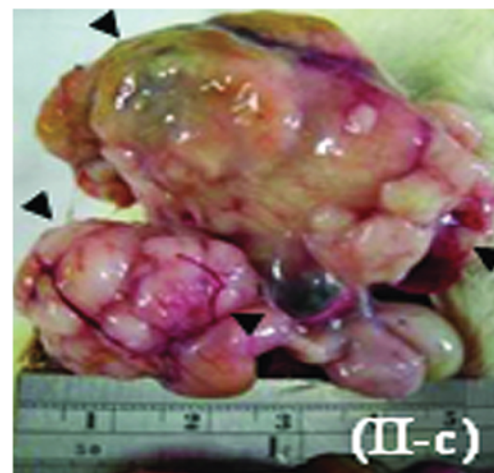
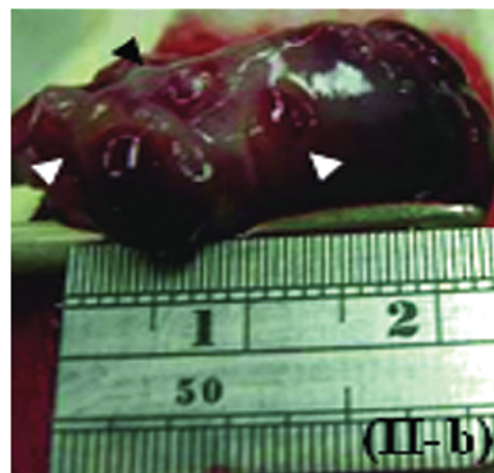
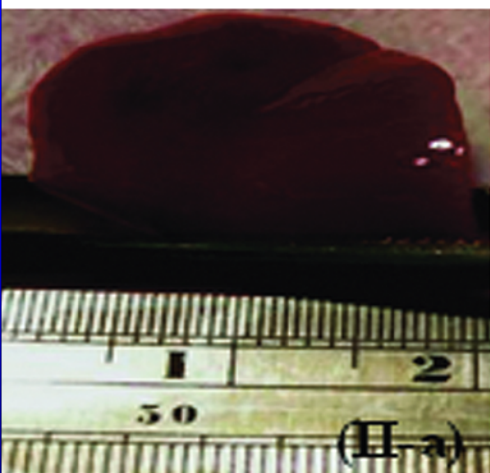
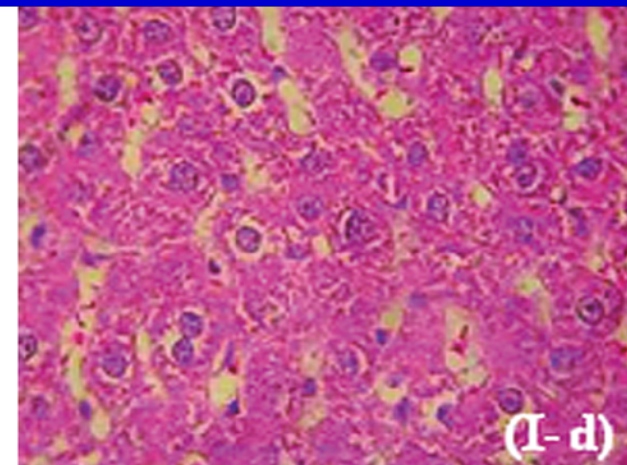
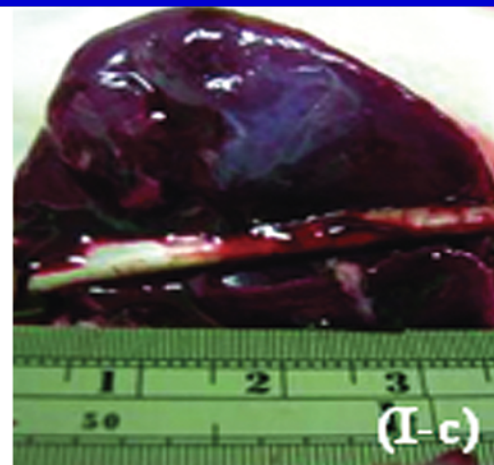
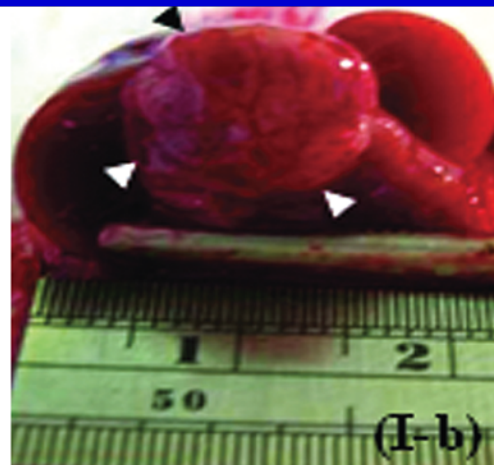
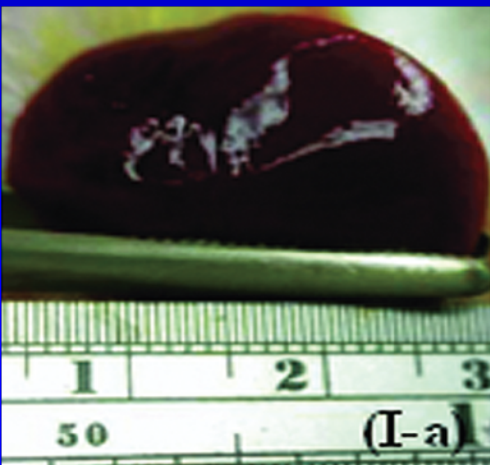
37 MBq /rat

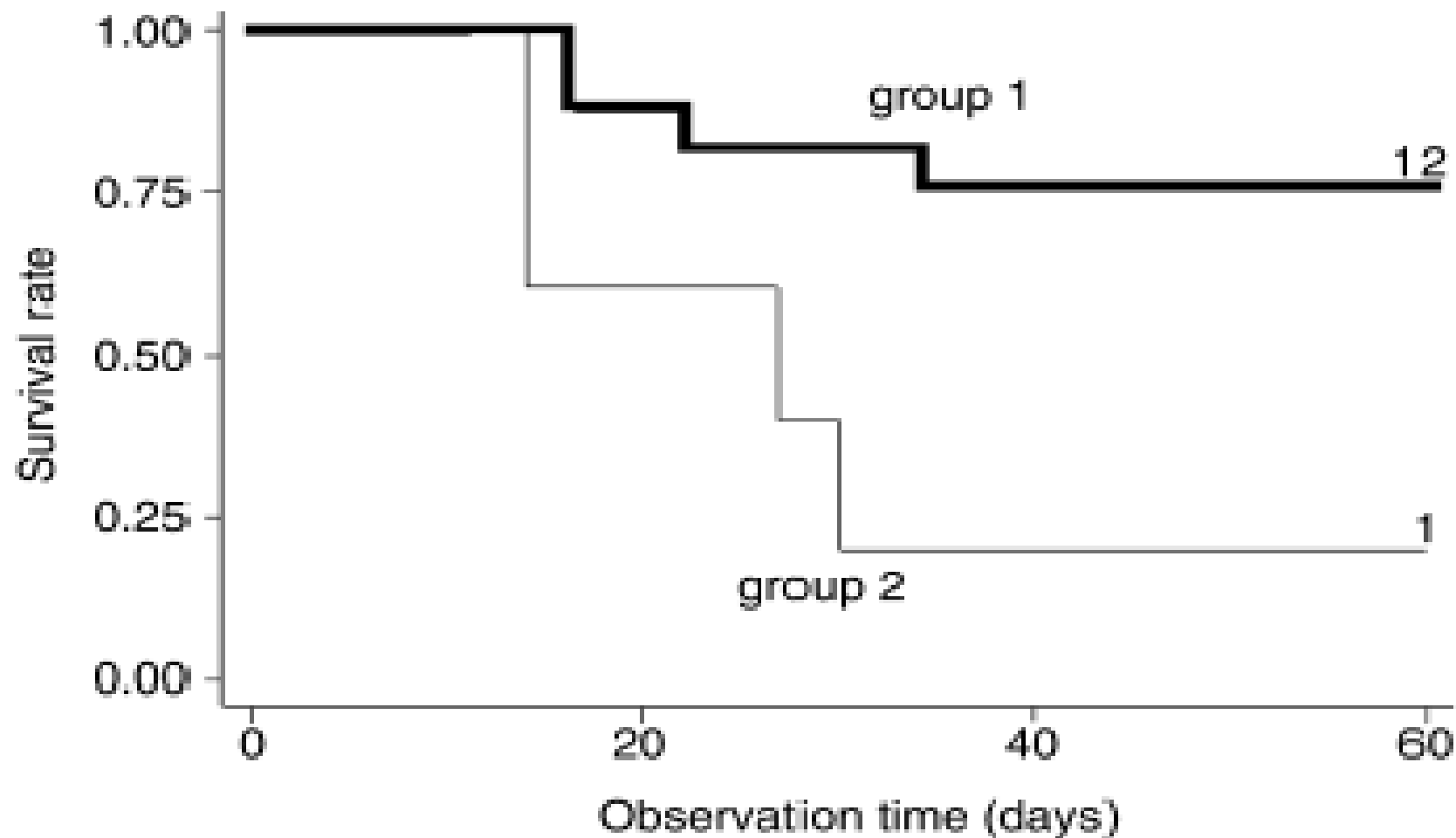
\*Tumor was assumed to be ~2 cm in diameter.





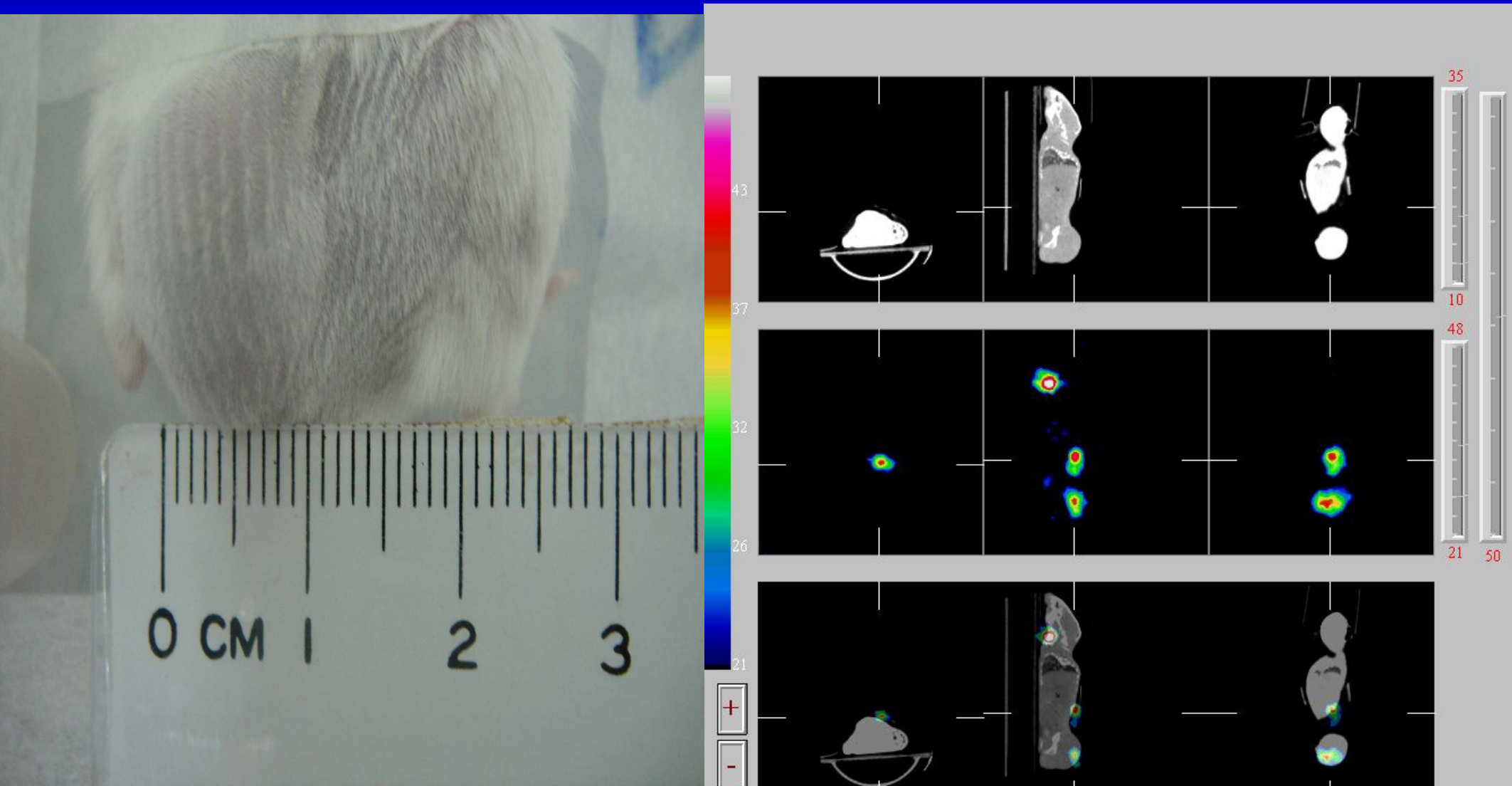
# 188Re-ECD/Lipiodol as a Therapeutic Radiopharmaceutical by Intratumoral Injection for Hepatoma Treatment






Group I: Rhenium 188 ECD/Lipiodol treated group, activity:  $30.4 \pm 21.8$  MBq/0.1 mL, N= 29, tumor weight  $655.2 \pm 438.7$  mg  
 Group II: control group, N=10, tumor weight:  $639.4 \pm 271.9$  mg

# Implants or In Situ Gelling System for Radiopharmaceutical Delivery



# Rhenium-188 based Radiopharmaceuticals for Treatment of Hepatoma

- The formula— solution, HDD/Lipiodol, ECD/Lipiodol or else, but approved from our TFDA
- The delivery method— local approach or arterial approach  recruit of different patients
- Clinical trials— INER sponsored and driven, or PI initiated, single or multi-centers

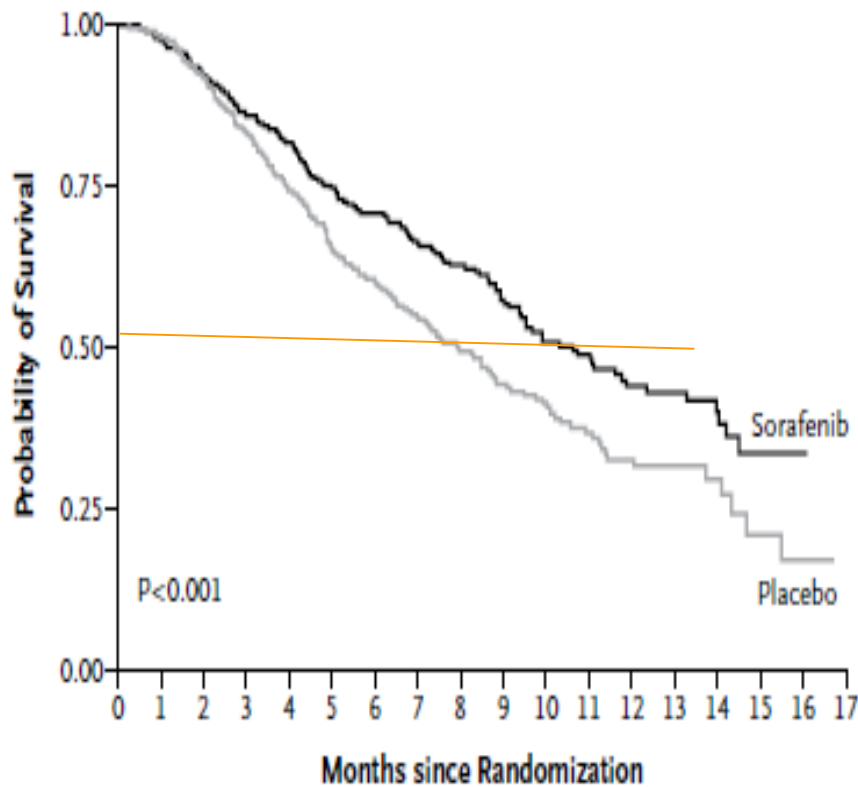


# Clinical trials with sorafenib in different patient group

European study

Taiwan study

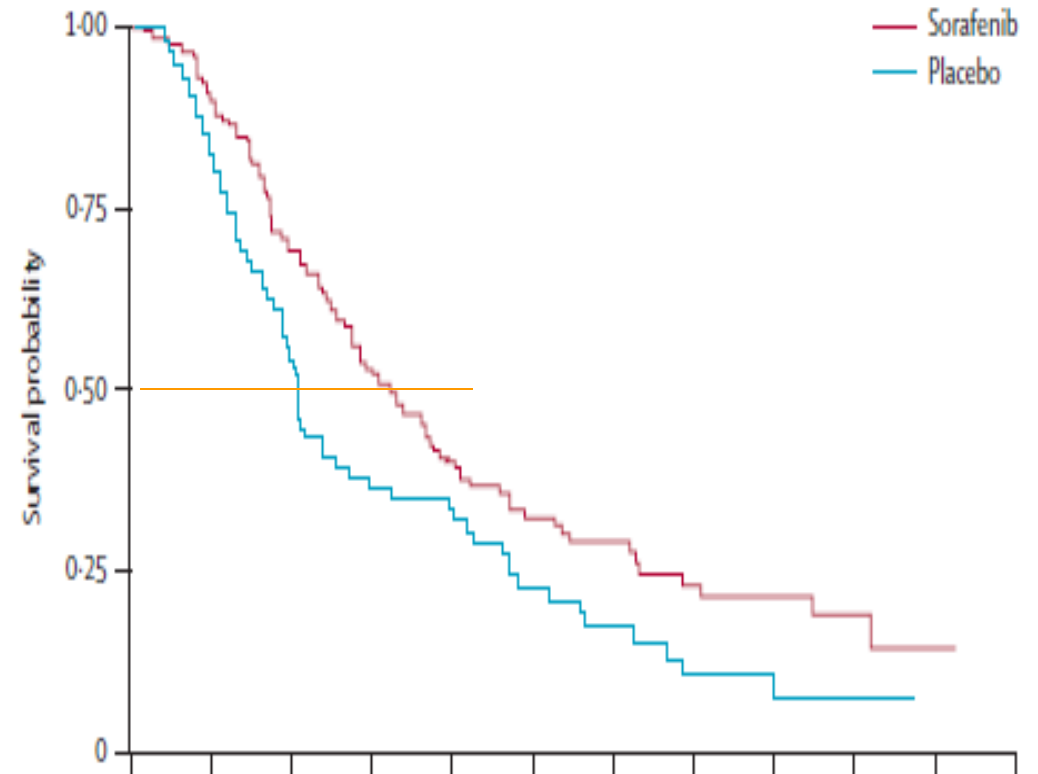
A Overall Survival



No. at Risk

Sorafenib	299	290	270	249	234	213	200	172	140	111	89	68	48	37	24	7	1	0
Placebo	303	295	272	243	217	189	174	143	108	83	69	47	31	23	14	6	3	0

A



Number at risk

Sorafenib	150	134	103	78	53	32	21	15	13	4	1	0
Placebo	76	62	41	26	23	15	9	5	4	1	0	0



# **Rhenium-188 based Radiopharmaceuticals for Treatment of Hepatoma**

- Efforts and experience from Y-90
- Monoclonal antibody-based drugs for Re-188
- More animal studies vs. clinical trial initiation
- **Team for clinical trial conduction**

# Case-Inclusion, exclusion criteria

(適合病例)

送件；專案申請進口用藥

專案申請進口用藥

住院

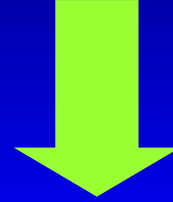
Pre-treatment  
screening evaluation

如符合lung/liver ration <15%

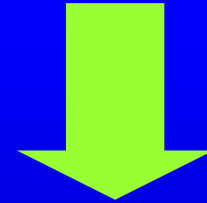
下order，買藥

Hepatic angiography  
protective embolization  
MAA-99mTC

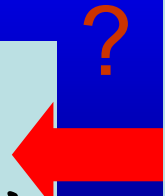
找單人病房；與Radiologist約時間



下order 後第五天，藥入台灣，2天內  
要打入病人體內，通常 $\leq 3$  GBq Y-90



不需special nurse；照顧不需  
隔離。治療三天內與他人保持  
兩公尺以上，隔天可出院



Radioprotection  
出院前輻射安全測試

? 15%  $\gamma$ -ray

Re-188

