

# Intra-arterial Radionuclide therapy

Prof John Buscombe

# Disclosures

- Consultancies
  - Navidea
  - Eli Lilly
  - MSD
- Paid lectureships
  - Sirtex
  - BTG
  - Bayer

# Who am I

- First appointed Consultant in Nuclear Medicine Royal Free Hospital, London 1994
- Cambridge since 2010
- Have performed >500 I-131 Lipiodol therapies
- Help set up IAEA Re-188 Lipiodol project
- Over 70 SIRTS
- Wrote file for licensing SIR-Spheres<sup>®</sup> and TheraSphere<sup>®</sup>
- Published 12 papers on liver i/a treatment

# Plan

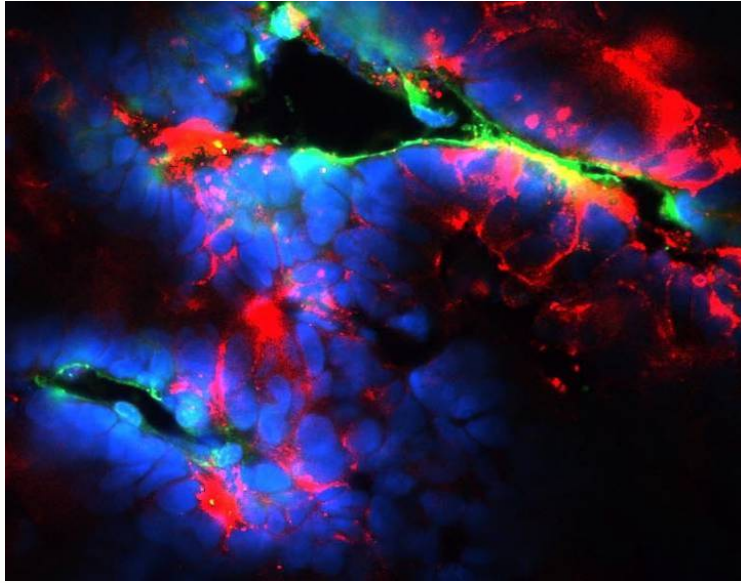
- Trying to treat CRC liver mets with radionuclide therapy-A5B7
- Pioneering I/A radionuclide therapy Lipiodol in HCC
- Y-90 vs I-131
- Use of Y-90 particulates in primary and secondary liver cancers-CRC
- Guidelines

# RIT colon cancer

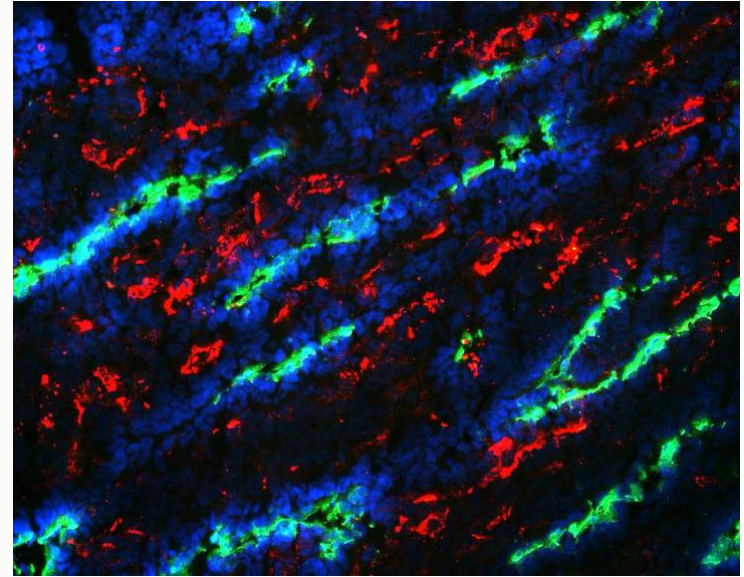
- Renda et al 1987 B72.3 (mouse IgG)
- Chung et al 1993 CEA-79 (mouse IgG)
- Pedley et al 1995 MFE-23 (humanised scVF)
- Green et al 1997 A5B7 (mouse IgG)
- Murray et al 2004 CC-49 (mouse IgG & ScVF)

# Movement of A5B7 over time in SW1222 xenografts

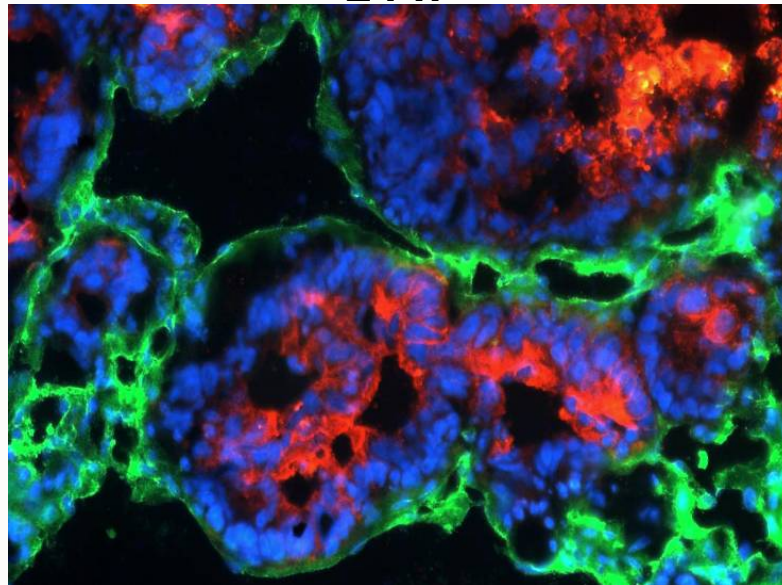
5 min



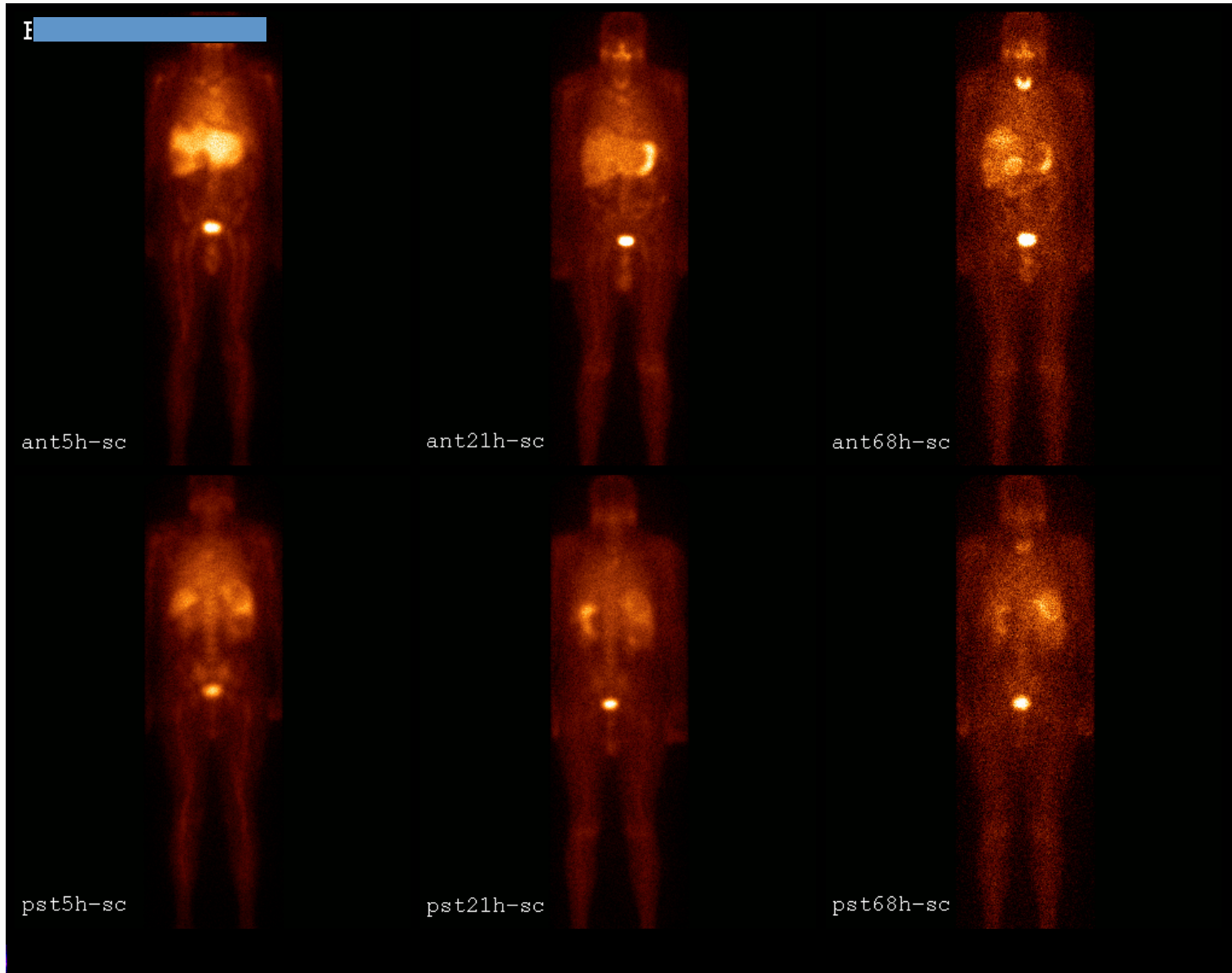
1- 24 h



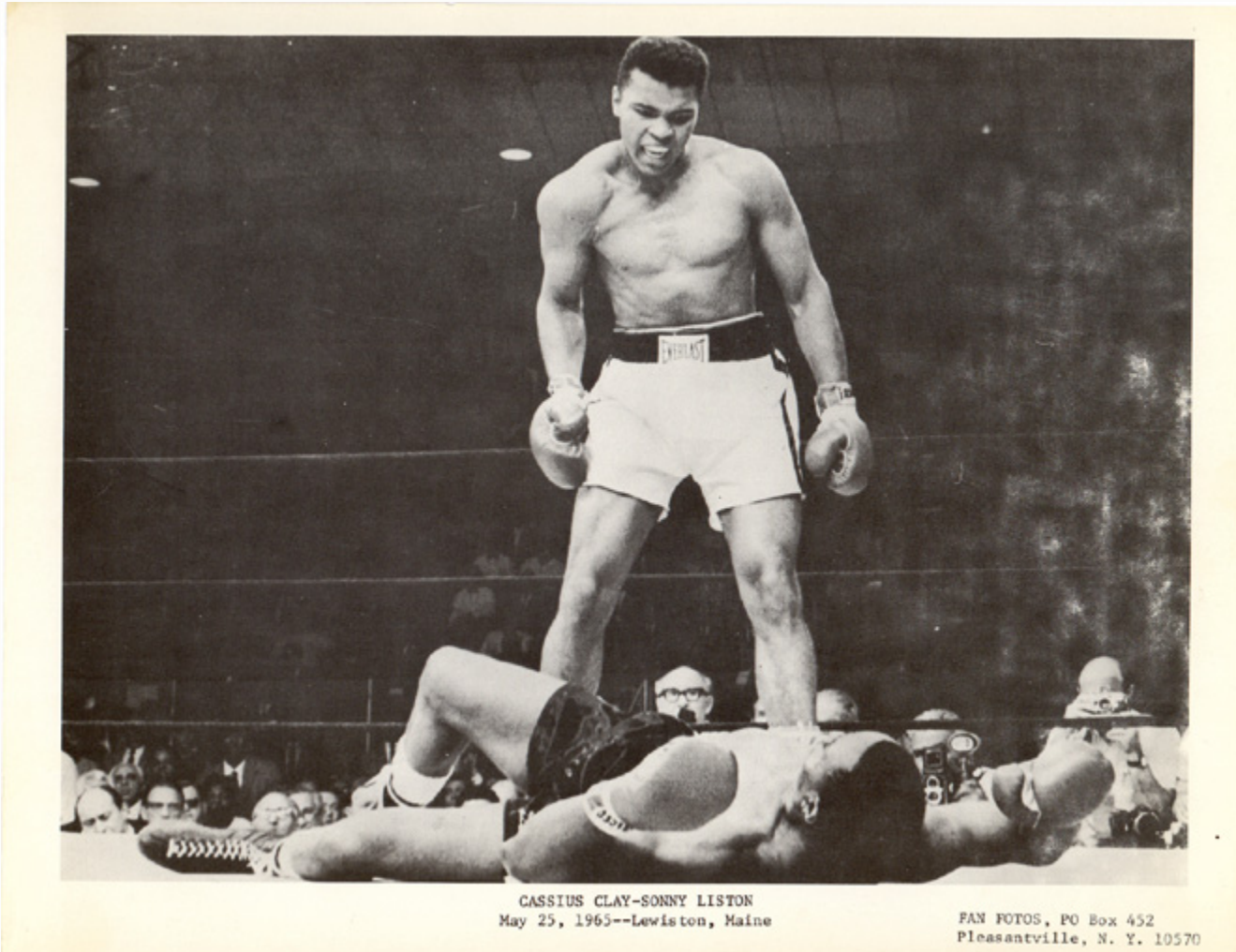
24 h



# 04DB SPECT Images A5B7 Uptake



# A new idea the double whammy



CASSIUS CLAY-SONNY LISTON  
May 25, 1965--Lewiston, Maine

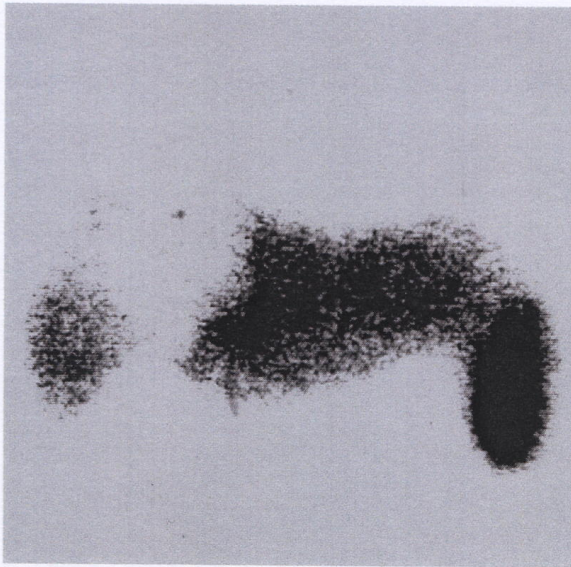
FAN FOTOS, PO Box 452  
Pleasantville, N. Y. 10570



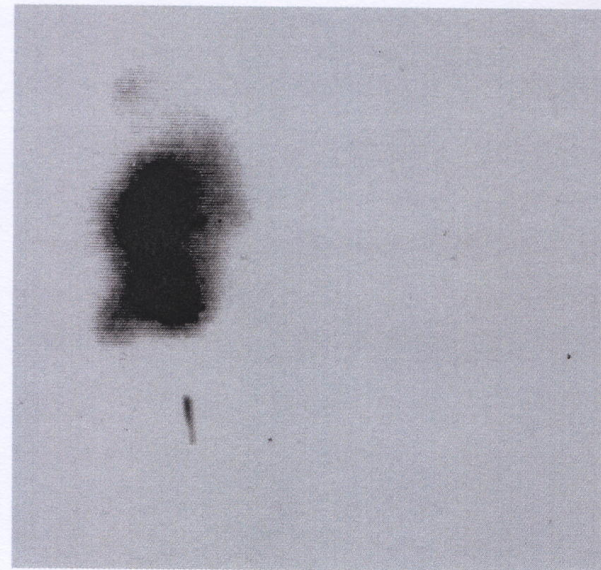
# 5 French catheter in the RHA



# Uptake of Lipiodol in HCC

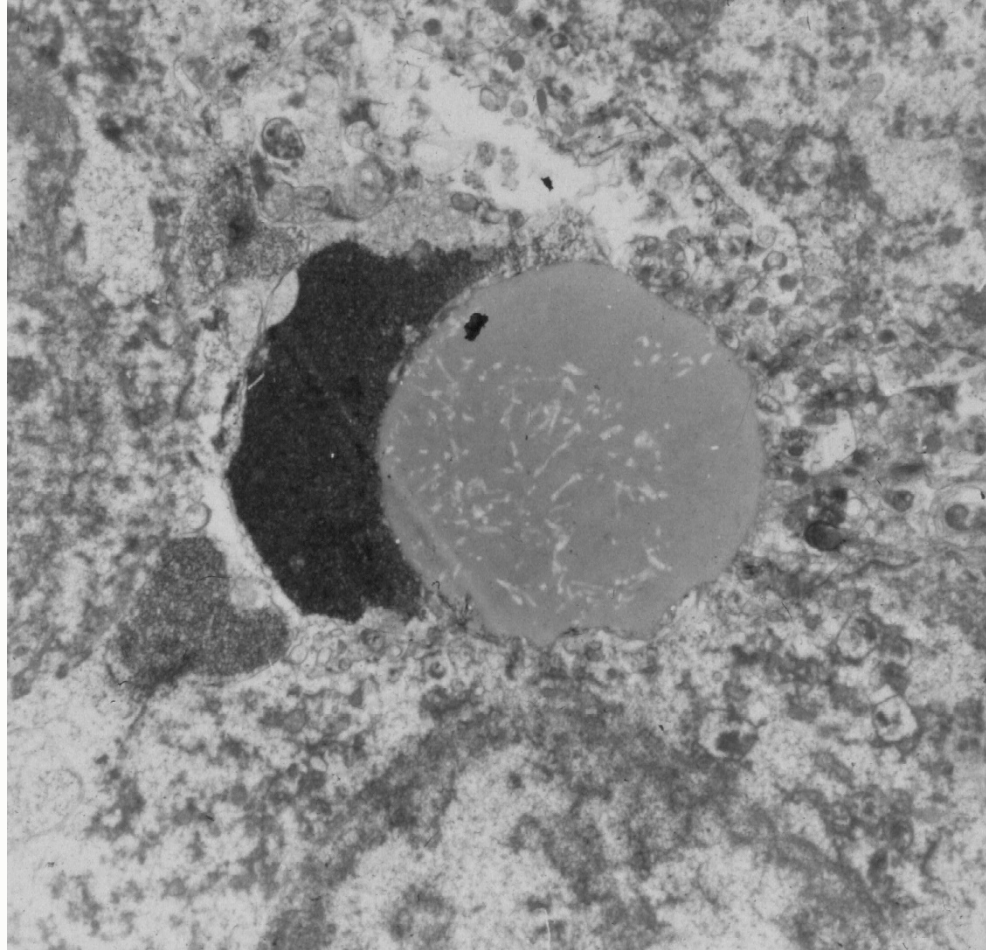


Tc-99m colloid scan  
showing defect at site of  
Liver cancer



Scan performed after I-131  
Lipiodol therapy in same  
patient showing uptake only  
in the liver cancer

# Lipiodol in HCC cell

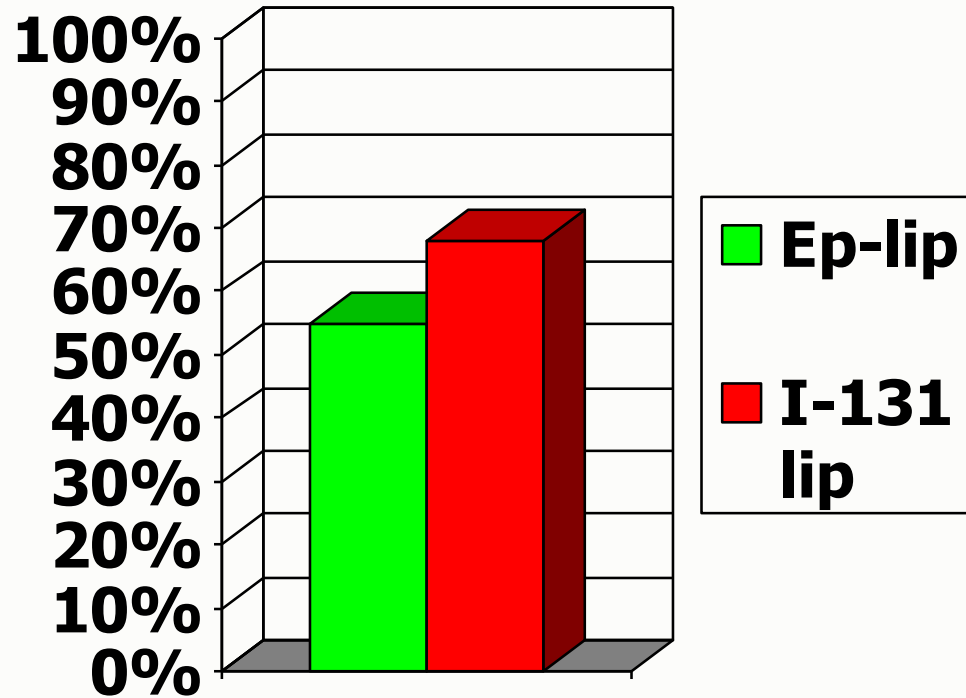


# Battacharya et al Cancer 1995

- ▶ Randomised trial comparing epirubicin Lipiodol and I-131 Lipiodol
- ▶ 86 patients with epirubicin
- ▶ 37 I-131 Lipiodol
- ▶ Imaging at 48 hours to determine residence
- ▶ Response rate and survival measured

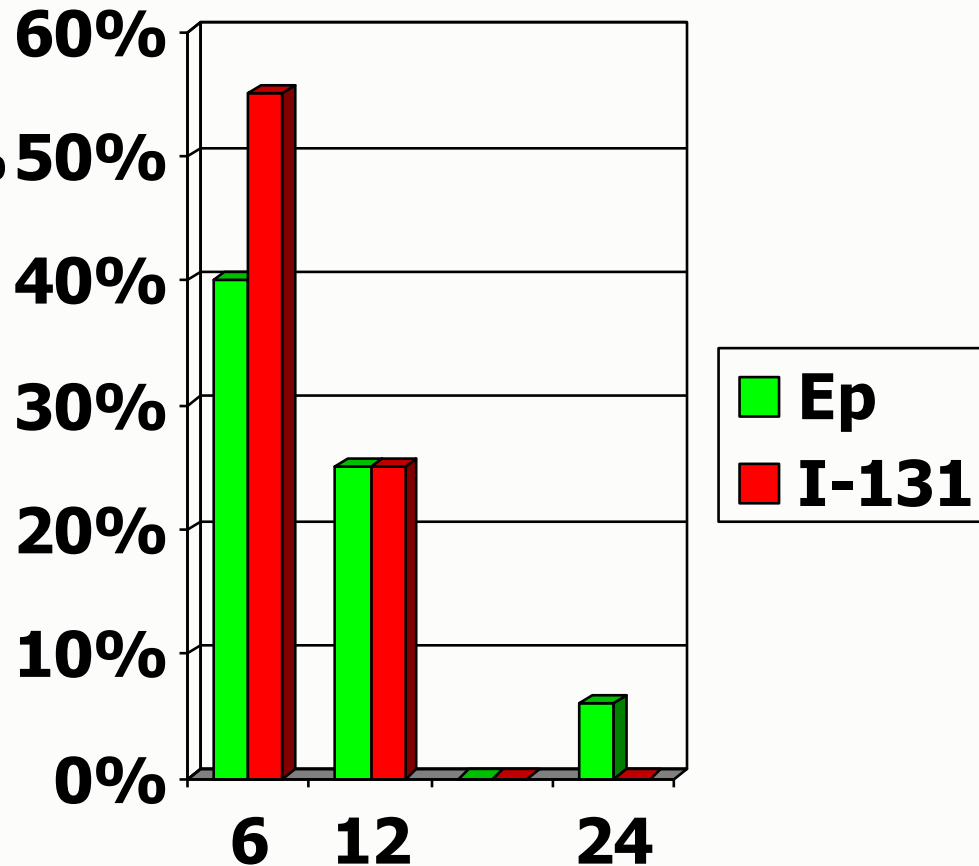
# Response rate

- ▶ Measured by change in size of tumour on CT
- ▶ Any new tumours counted as progression
- ▶ All patients in DP when treatment given



# Survival

- ▶ Survival determined at 6, 12 and 24 months
- ▶ In this patient group 50% survival at 6 and 0% at 12 months expected



Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		6-m	1-year	2-year	Sign			
Raoul <i>J Nucl Med</i> 1994	[ <sup>131</sup> I]Lipiodol (60 mCi) via hepatic artery × 4 over 1 year: <i>n</i> = 14 No anticancer rx: <i>n</i> = 13	48%			<i>p</i> < 0.01	81% etoh 48% Child's B 52% Child's A	75% main PVT 25% branch PVT	
Order <i>Int J Radiat Oncol Biol Phys</i> 1991	[ <sup>131</sup> I]Antiferritin + doxorubicin 15 mg + 5-FU 500 mg q8 wk: <i>n</i> = 48 Doxorubicin 60 mg/m <sup>2</sup> + 5-FU 500 mg/m <sup>2</sup> q3 wk: <i>n</i> = 50	No dif.			NS	Not stated	No met.	
Bhattacharya <i>Cancer</i> 1995	[ <sup>131</sup> I]Lipiodol via hepatic artery: <i>n</i> = 11 Lipiodol + epirubicin 75 mg/m <sup>2</sup> via hepatic artery: <i>n</i> = 17	58%	25%	0%	NS	Child's A and B	No PVT	
Raoul <i>Hepatology</i> 1997	[ <sup>131</sup> I]Lipiodol via hepatic artery × 5 over 18 m: <i>n</i> = 65 TACE (including cisplatin 70 mg) × 5 over 18 m: <i>n</i> = 64	69%	39%	22%	NS	74% etoh 75% Child's A	50% unifocal 24% tumor involving >50% of liver volume	27% life-threatening toxicity and 9% fatal toxicity in TACE arm
		66%	42%	22%				

TACE = transarterial chemoembolization; m = month; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; etoh = alcohol-induced liver disease; rx = therapy.

J. D. Schwartz and A. S. Beutler. *Anticancer Drugs* 15 (5):439-452, 2004.

# New data

- ▶ Marelli et al 2009 JNM
- ▶ Reviewed results of 124 patients treated for HCC, 50 with I-131 Lipiodol 1996=2007
- ▶ No survival difference between TAE, TACE and I-131 Lipiodol
- ▶ In patients with PVT
  - Mean survival TAE/TACE = 171 days
  - Mean survival I-131 Lipiodol = 454 days
- ▶ In patients with advanced disease
  - Mean survival TAE/TACE = 36 days
  - Mean survival I-131 Lipiodol = 363 days



# Learning points

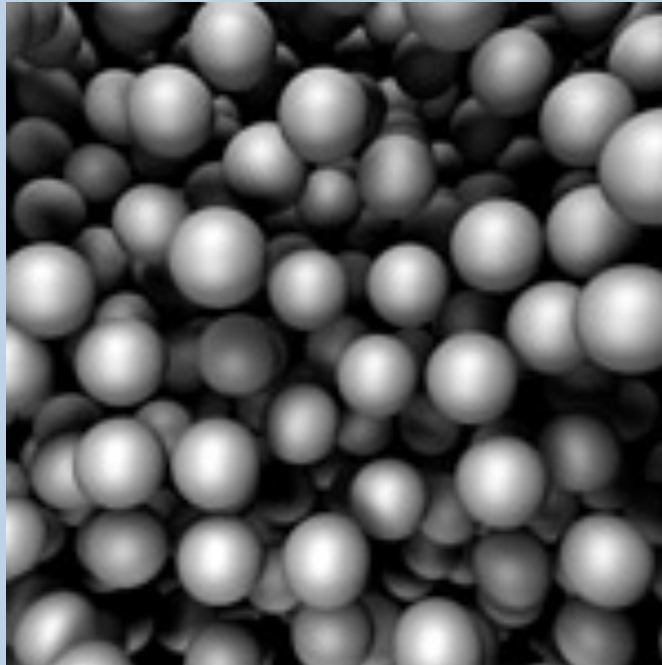
- Successful treatment needs teams
  - Oncologist
  - NM Physician
  - NM Physics
  - Interventional Radiologist
- Rare in 1995, much more common now
- Need a bigger bang for our buck-new isotope

# Y-90 particulates

2 main types

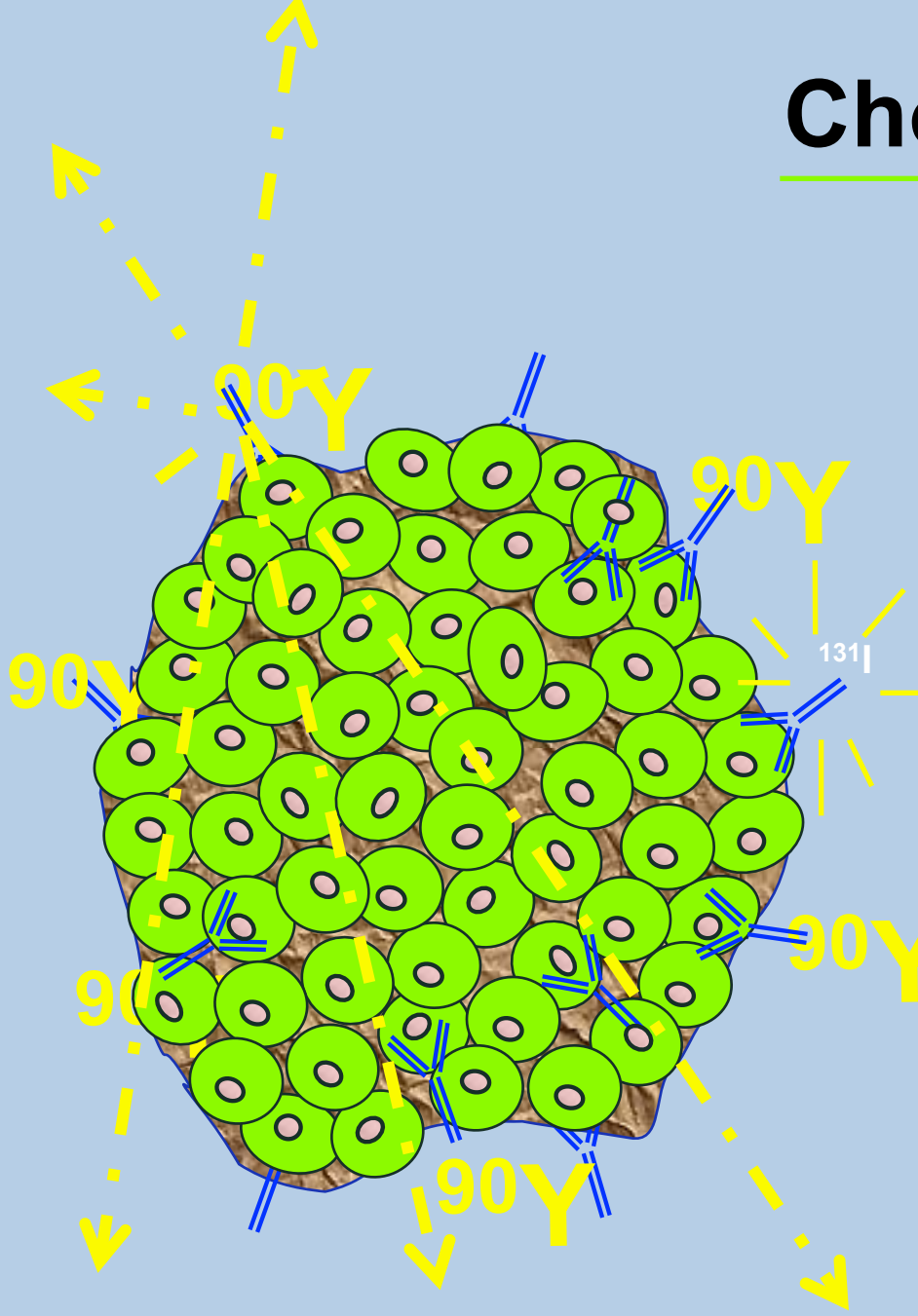
From Australia Y-90 resin balls SIR-Spheres<sup>®</sup>

From Canada Y-90 integrated glass balls TheraSphere<sup>®</sup>



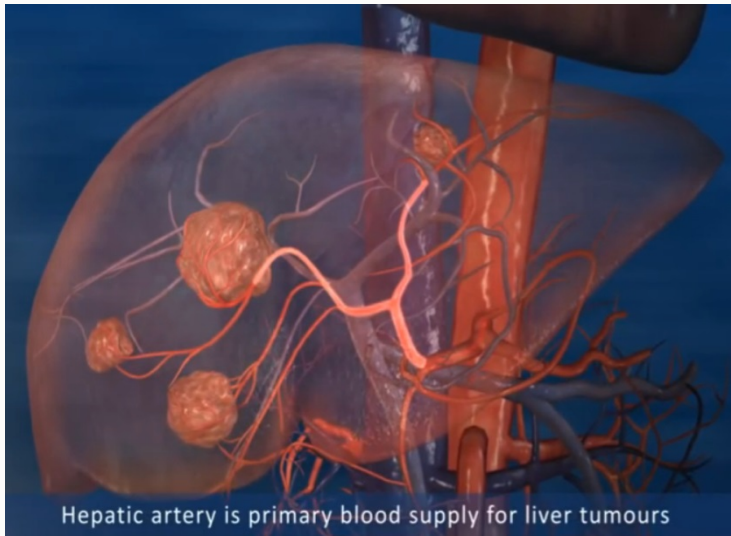
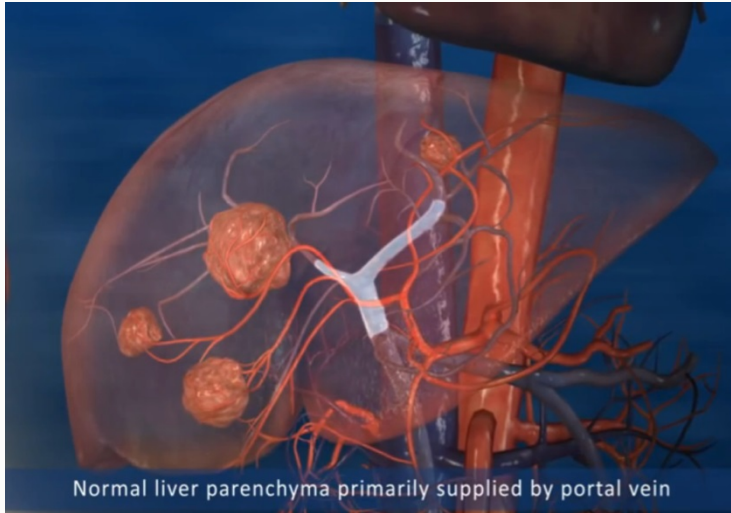
# Choice of Isotope

⇒ Higher beta energy and longer path length of  $^{90}\text{Y}$  make it an optimal isotope for radioimmunotherapy



Properties	$^{90}\text{Y}$	$^{131}\text{I}$
Energy	Beta emitter (2.3 MeV)	Gamma (0.36 MeV) Beta (0.6 MeV)
Path length	$\chi_{90}$ 5 mm	$\chi_{90}$ 1 mm
Administration	Outpatient	Inpatient or restrictions to protect family/ environment
Half-life	64 hours	192 hours
Urinary Excretion	Minimal 5% 7 days	Extensive/variable 48% - 90% in 48 hours

# Y-90 particulates

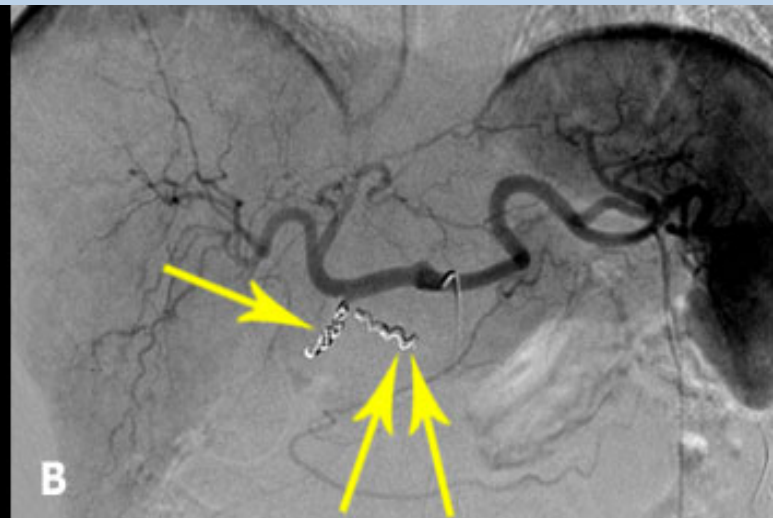
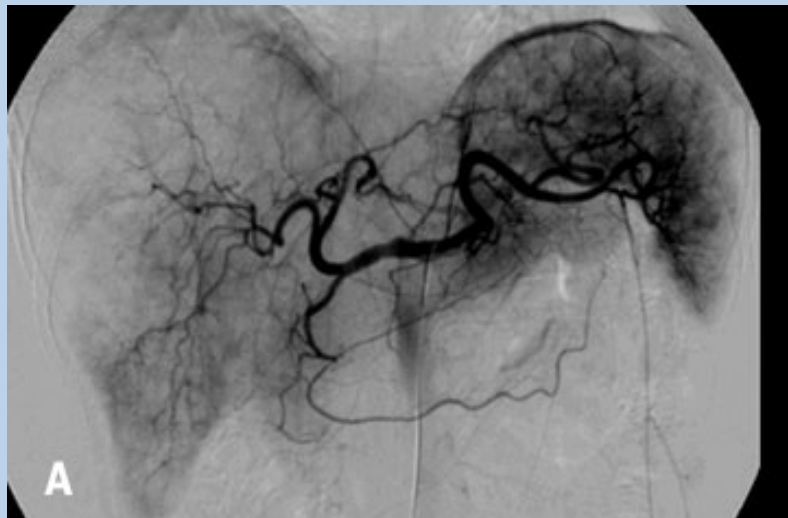


- Non resectable liver tumour is a management challenge
- External beam radiation unable to deliver an effective dose (90Gy for most adenocarcinoma) without damaging surrounding parenchyma
- Y-90 is a beta emitter, deliver a target dose of  $> 100\text{Gy}$ , penetrates about 11mm in soft tissue
- Half life 64.1 hour

# How do you give SIRT

- ▶ Day 1
- ▶ Need to block off collaterals including GDA with coils
- ▶ Prevents Sir spheres going to stomach or pancreas
- ▶ Inject 80-100MBq Tc-99m MAA into radiological catheter and flush line
- ▶ Image to determine shunt
- ▶ Also consider SPECT/CT

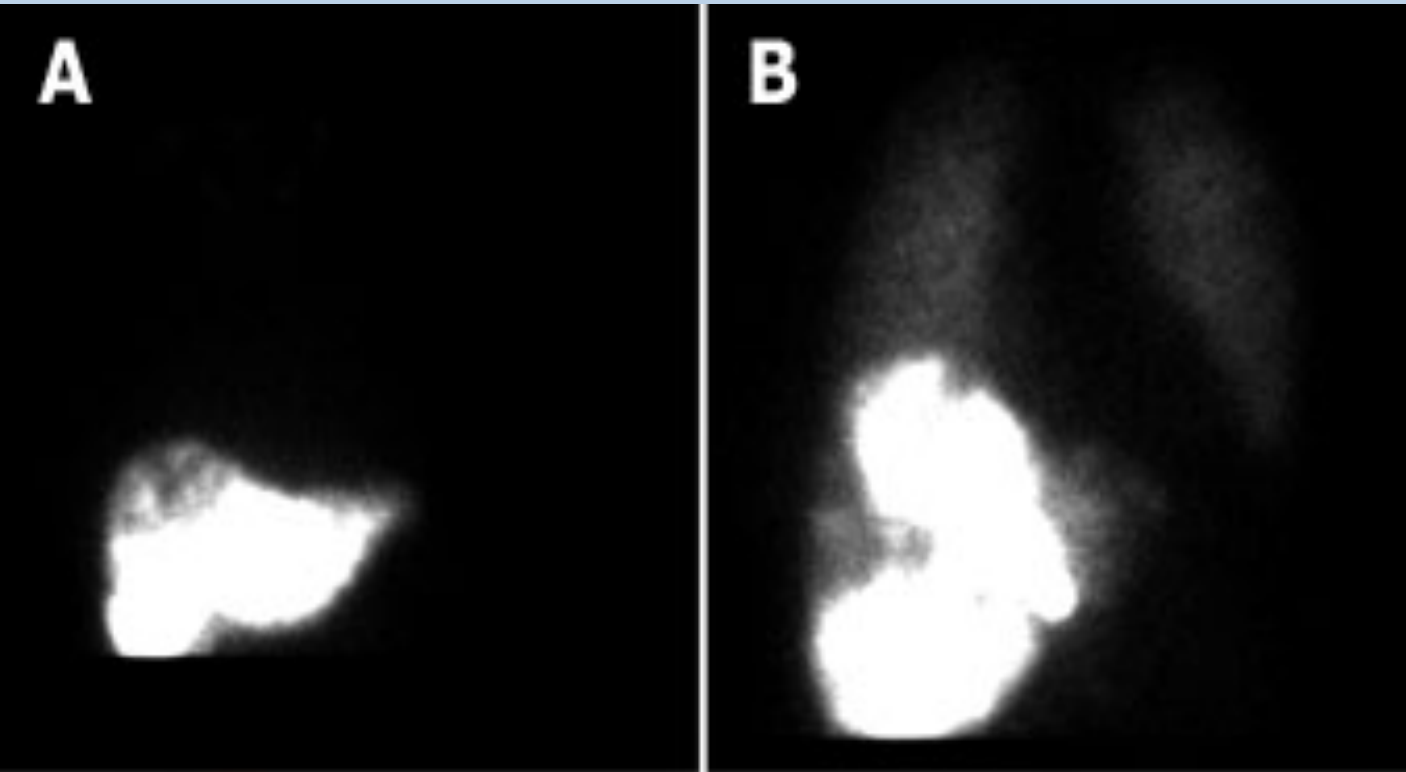
# Removing collaterals



# Calculating shunting

- ▶ 2 main problems with SIRT
- ▶ If too much shunt to lung leads to radiation pneumonitis
- ▶ Also in some patients shunting to small bowel/stomach often via small vessels
- ▶ All can be calculated from MAA scan
- ▶ In both TheraSphere<sup>®</sup> and Sir-Spheres<sup>®</sup> lung shunting >10% can modify results

# Shunting

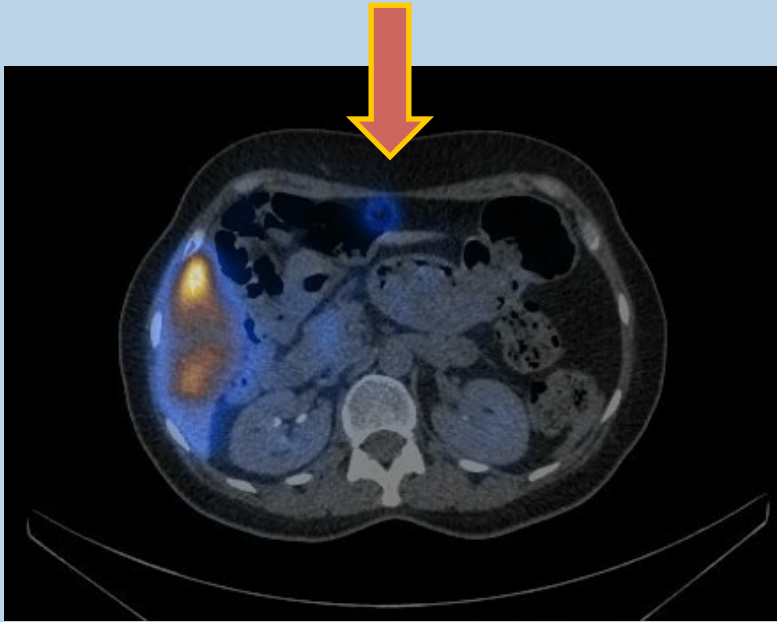


No shunting

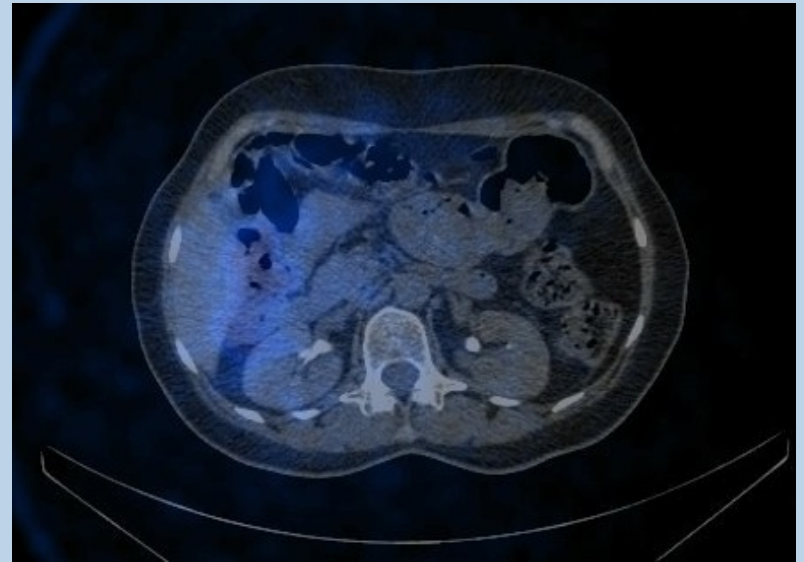
27% shunting



# Finding extra-hepatic uptake



Tc-99m MAA shows uptake in a falciform artery



Y-90 SIRT

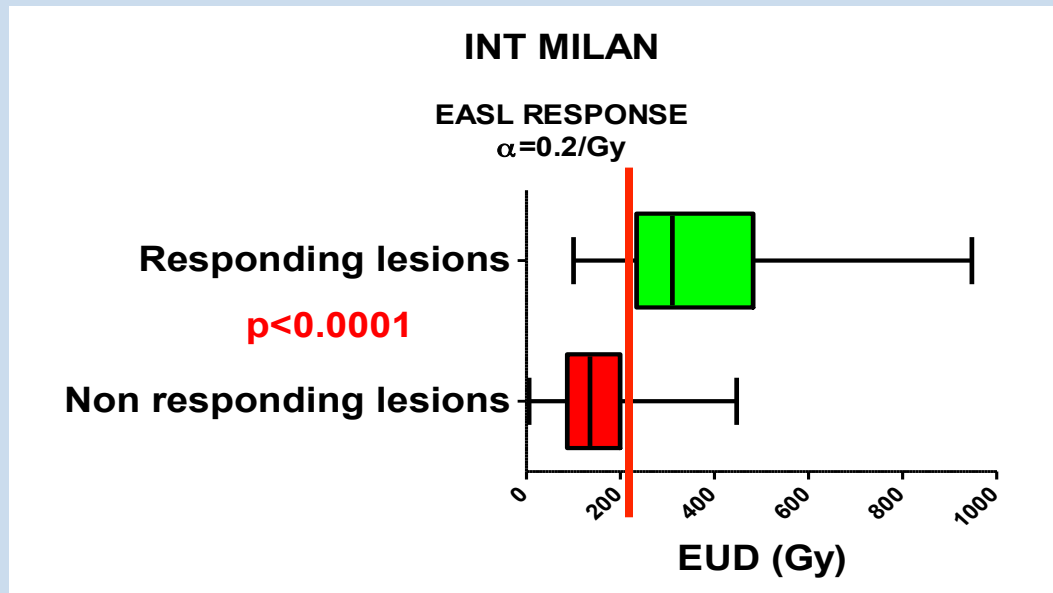
# Picking the activity for SIRT

## ▶ 3 methods

- Individual dosimetry based on MAA scan +/- SPECT  
keep lung dose below 30Gy
- Semi empirical
  - ▶ Degree of shunting
  - ▶ Size of patient-BSA
  - ▶ % liver full of tumour
- Fully empirical Give 2-3GBq

## ▶ No good evidence which is best

# <sup>90</sup>Y-microspheres/ Chiesa C. et al. EANM 2010



Courtesy C. Chiesa, Milan

- dose response relationship exists for the tumour: importance of EU

*Inhomogeneity is different for SIR-Spheres<sup>®</sup> compared to TheraSphere<sup>®</sup>*

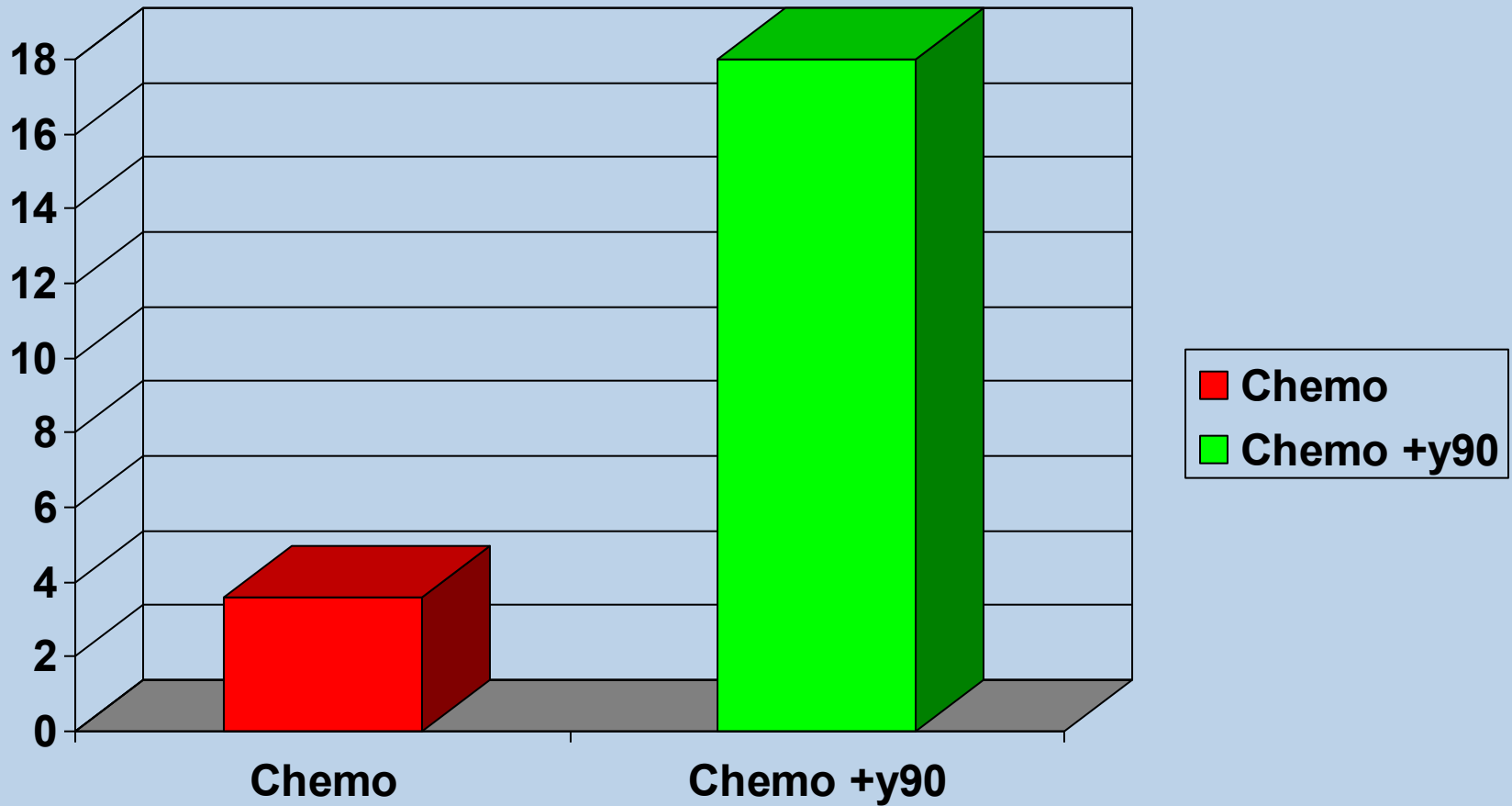
- no clear correlation for toxicity, in particular not a clue for well compensated cirrhosis

# Pivotal study

## van hazel JSO 2004

- ▶ Phase II RCT from Australia
- ▶ 21 patients metastatic CRC
- ▶ <25% liver mets >80% mets in liver
- ▶ All patients received 4 cycles of 5F-U and leucovorin
- ▶ Half randomised to additional Y-90 Sir-Spheres

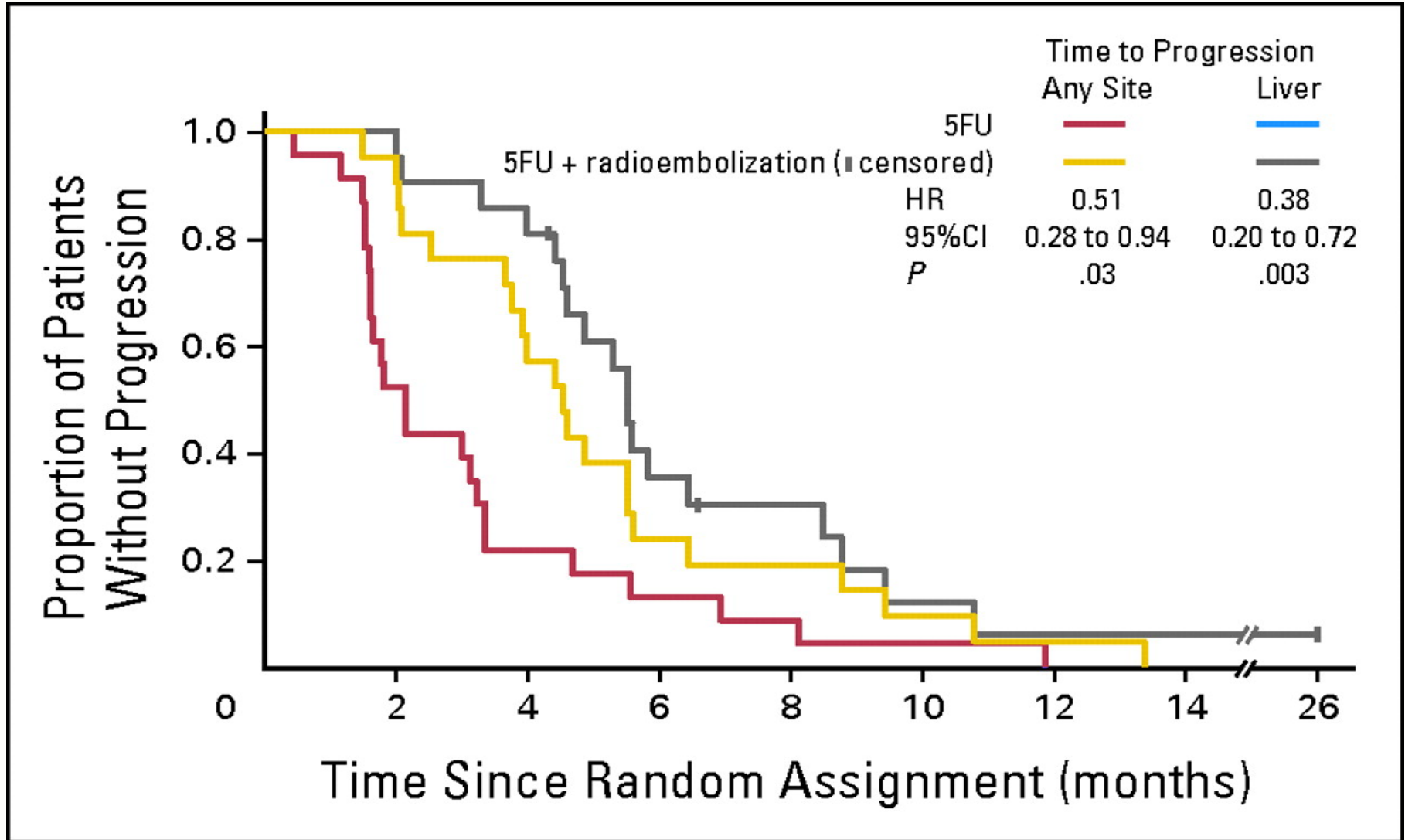
van Hazel et al 2004  
Median PFS (p=0.005)



# Confirmation

- Hendlisz et al J Clin Onc 2010
- Belgian study phase III 5FU vs 5FU+Y-90 SIRT
- 46 patients with unresectable CRC mets in the liver recruited but 44 assessed
- Median TTP was 2.1 months for 5FU and 4.5 months for 5FU and Y-90 SIRT (those not given SIRT were then given SIRT)
- Median OS was 7.3 months for 5FU vs 10 months for 5-FU and Y-90 SIRT

# Time to progression-Hendlisz JCO



# One patient's result

**Cambridge News**  
Wednesday, August 31, 2011 cambridge-news.co.uk 45p

**WIN** family days out at Cambridge  
Includes stadium tour and run-out with team

**WalkRunCycle** Make the most of life outdoors  
How to stay motivated The Effer Tower dash Our latest cycling blog

**Independent schools guide** Helping parents choose with 8-page pull-out

**My cancer miracle**  
Doctors who gave Brian just 12 months to live are amazed as tumours vanish under trial treatment

**JORDAN DAY**

ALMOST a year ago today, 72-year-old Brian Brooks was given just 12 months to live. It was discovered that the beloved father and grandfather had massive tumours in both his colon and liver. Even with gruelling chemotherapy, doctors at Addenbrooke's feared the tumours would not clear.

But Mr Brooks is now alive to tell the tale and in remission – after taking part in a groundbreaking trial launched by Cancer Research UK.

Speaking from their home in Nonesuch Lane, near Stuntney, Ely, Mr Brooks and his wife, Nicky, both committed Christians, described it as a "miracle".

Mr Brooks said: "To be told you have 12 months to live and then to have completely healed 12 months down the line, we believe, is a miracle.

"Obviously there is always the risk that cancer can come back but I am now in remission and that is something that doctors did not believe was possible."

It was on September 6 last year that Mr Brooks, a retired boarding kennel owner, was diagnosed with cancer of the colon and liver after he had randomly decided to undergo a bowel screening test at Addenbrooke's. It showed there was a huge tumour in his colon.

Further scans then showed the cancer had spread to Mr Brooks's liver. He was given just 12 months to live.

But it was when Mr Brooks was about to start his chemotherapy

**IN REMISSION:** Brian Brooks at home with his wife Nicky. Pictures: Richard Patterson 765835



that a nurse mentioned a special trial, called Foxfire, had been launched.

The trial, spearheaded by Cancer Research UK and the Bobby Moore Fund, was testing a new treatment called Radioembolisation, a form of internal radiotherapy that uses the tumour's blood supply to target multiple sites of disease within the liver.

Mr Brooks put his name forward – and to his shock, was one of hundreds of people to be picked to take part.

Mrs Brooks, 67, said: "Again, it was completely random – Brian's name was picked and he underwent the trial alongside his chemotherapy.

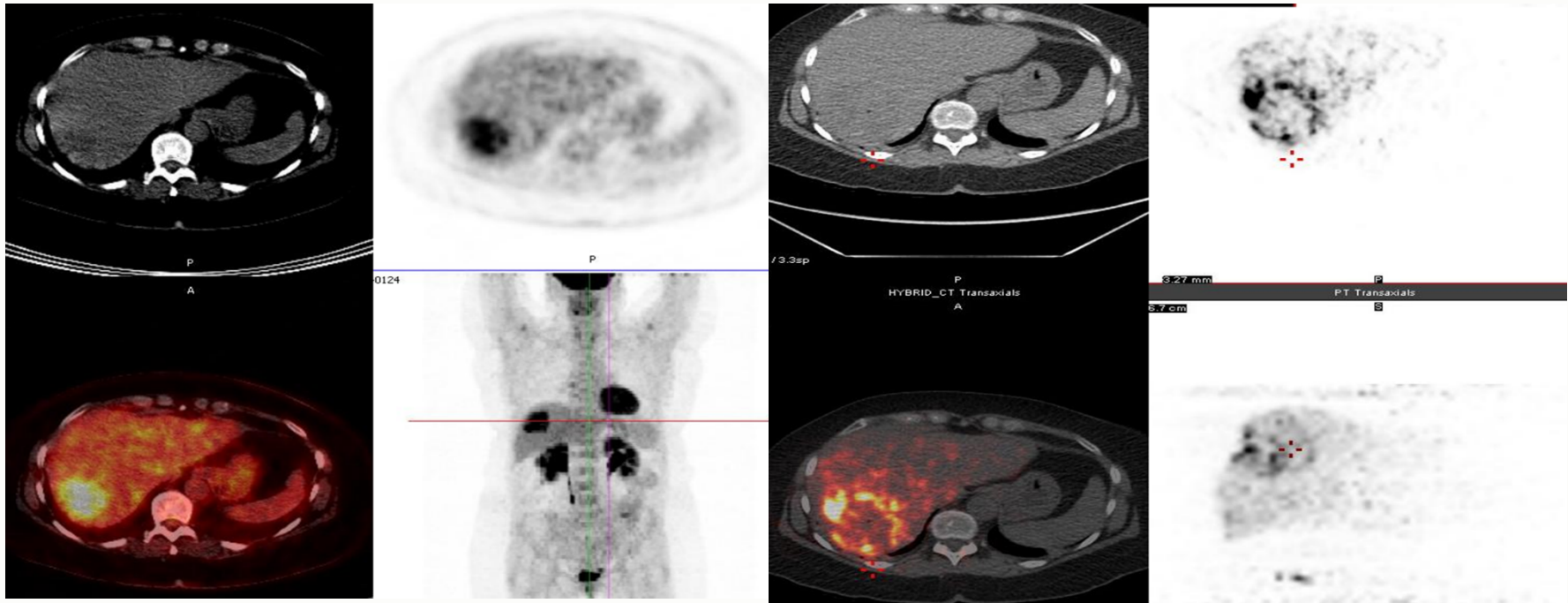
"We've just had the results back and Addenbrooke's can't believe

■ Turn to page 5

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# TOF PET-CT



Patient with large metastases in the posterior right lobe of the liver but unable to have surgery due to co-morbidities. The FDG PET shows the single liver metastases the Y-90 PET-CT shows the particles surrounding the tumour

# SIR-Spheres<sup>®</sup> trials

Name	Disease	Comparison	Comment
Foxfire	1 <sup>st</sup> line Ca Colon	5FU+ox+folonic +/- SIRT	Closed
SirFLOX	1 <sup>st</sup> line Ca Colon	FOLFOX +/- SIRT	Closing
Foxfire global	1 <sup>st</sup> line Ca Colon	FOLFOX+Bev +/- SIRT	Open
SIRIUM	Melanoma mets	Sorafenib +/- SIRT	Open
Soramic	Unresectable HCC	Sorafenib +/- SIRT	Open

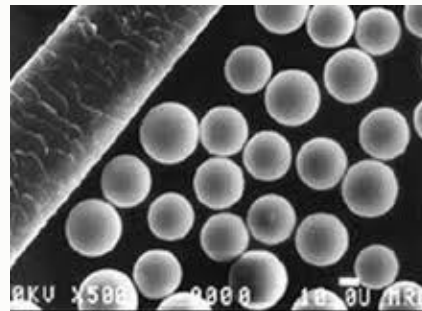
# TheraSphere<sup>®</sup> Manufacturing Process

**<sup>90</sup>Y is integrated into the glass matrix:**

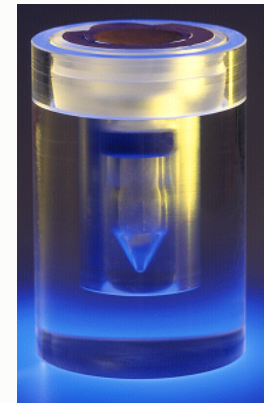
- Results in high activity per microsphere<sup>1</sup>
- High product stability<sup>2</sup>: <sup>90</sup>Y is not surface bound
- Minimizes risk of vascular stasis ( due to low number of microspheres<sup>1</sup>)



**High-purity raw materials**  
40% Y<sub>2</sub>O<sub>3</sub>, 20% Al<sub>2</sub>O<sub>3</sub>, 40% SiO<sub>2</sub>

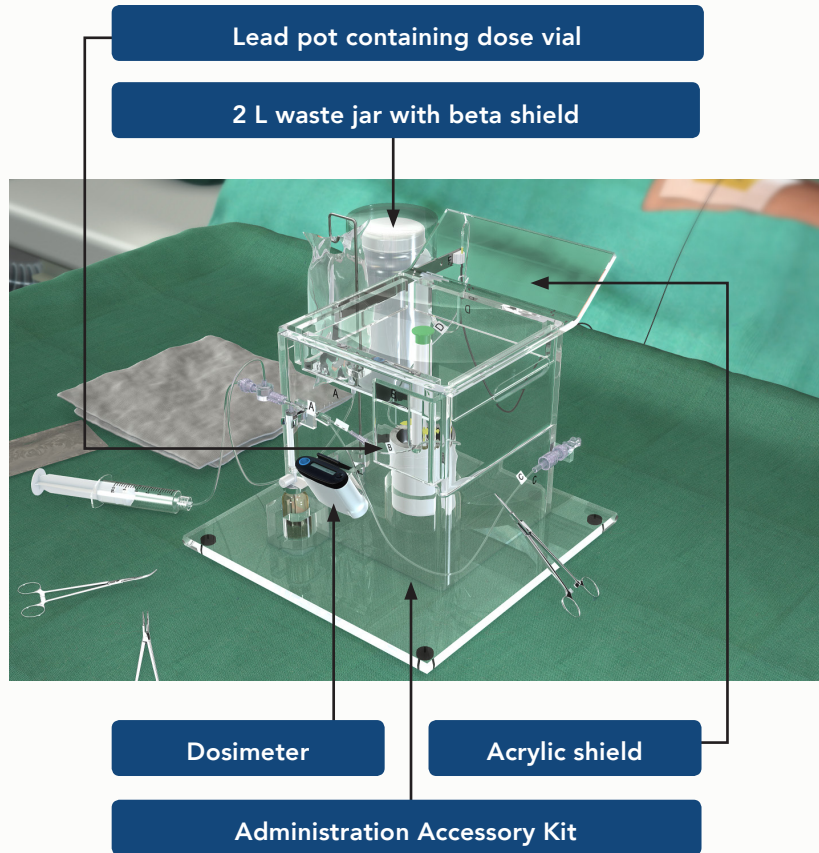


**Melt and Spheroidize**



1. TheraSphere<sup>®</sup> US PI 2014. 2. Erbe, E.M., Day, D.E. J Biomed Mat Res (1993) 27; 1301-1308.

# TheraSphere® Administration Accessory Kit Design



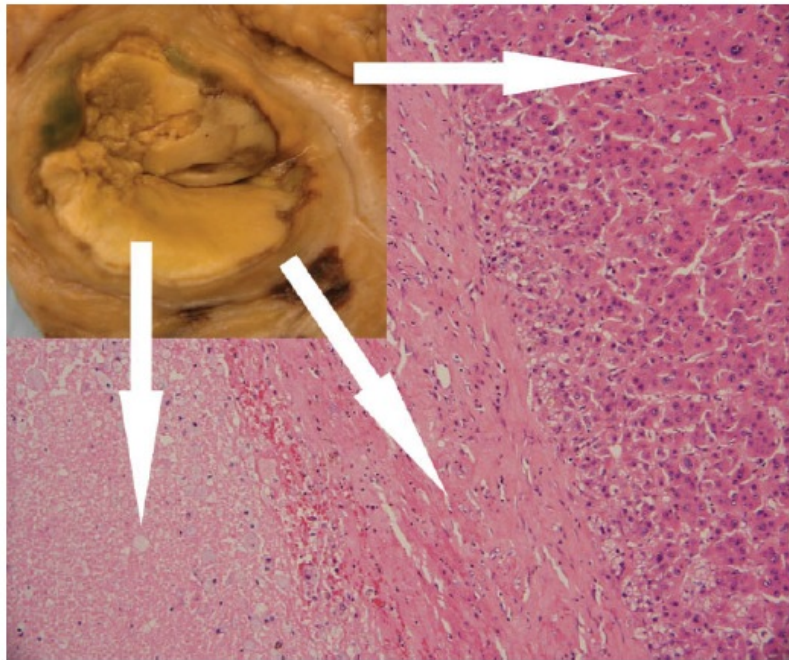
## TheraSphere® Administration Accessory Kit

- Provides 100% beta shielding to the user through the acrylic shield
- Is supplied with a 2 L waste jar beta shield for handling and storing post-treatment waste
- Is designed to contain any potential leaks from the dose vial (although leaks are exceedingly rare)

# TheraSphere® Administration Accessory Kit Design



# Post treatment

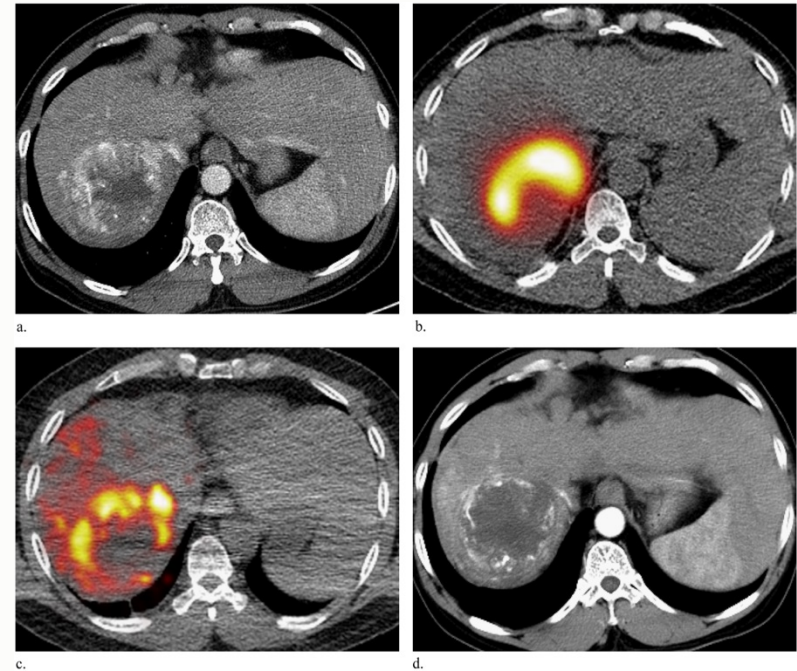


## HCC tumour

A Normal Parenchyma

B Fibrosis (Peripheral Rim)

C Complete Necrotic tumour



## 6 cm Right Lobe HCC

A Baseline CT

B Bremsstrahlung SPECT/CT

C PET/CT

D CT 1 month post treatment

# History of Treatment with Y90 Microspheres

- There is a long history of using Y90 microspheres to treat hepatocellular carcinoma
- Blanchard 1989 (Can Assoc Radiol J) – liver metastases and hepatoma
  - Treatment with resin Y90 microspheres resulted in liver tumour volume reduction in 7/15 patients, including reduction of >50% observed in 5 patients
  - Mean survival was extended to 62 weeks vs. 30 weeks in Y90-treated and untreated patients, respectively
  - Gastritis or gastric ulceration occurred in 6/15 patients (in 3 cases due to unintended infusion of Y90 into gastric circulation)

# Glass Y90 Microspheres for Liver Metastases from CRC: Overview of Studies

Publication	No. of patients	Population	Outcomes	Safety
Sato <i>et al.</i> (2008)	137 (CRC: 51)	<ul style="list-style-type: none"> <li>• Unresectable, chemorefractory, liver metastases</li> <li>• Primary site: CRC (37%), breast (15%), NET (14%), ICC (5%), etc.</li> <li>• Median age: 61 yr</li> <li>• ECOG PS ≤1 (89%; 0: 60%; 1: 29%)</li> <li>• Extrahepatic metastases (50%)</li> <li>• Bilobar disease (80%)</li> <li>• Tumour burden ≤25% (80%)</li> <li>• Median <sup>90</sup>Y dose: 112.8 Gy</li> </ul>	<ul style="list-style-type: none"> <li>• ORR (WHO): 42.8%</li> <li>• ORR (PET): 90%</li> <li>• Median TTP: 462 d (15.4 mo)</li> <li>• Median survival: 300 d (10 mo; NET vs. CRC vs. Other: 776 vs. 457 vs. 207 d [25.9 vs. 15.2 vs. 6.9 mo])</li> <li>• 1- and 2-yr OS: 47.8% and 30.9%, respectively</li> </ul>	<ul style="list-style-type: none"> <li>• Fatigue (56%), abdominal pain (26%), nausea (23%)</li> <li>• GI ulcer (n = 1), radiation-induced cholecystitis (n = 1), bilomas (n = 2), hepatic abscess (n = 1)</li> </ul>

2. Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. *Radiology* 2008;247:507-515.



# Glass Y90 Microspheres for Liver Metastases from CRC: Overview of Studies

Publication	No. of patients	Population	Outcomes	Safety
Benson <i>et al.</i> (2013)	151 (CRC: 61)	<ul style="list-style-type: none"> <li>• Unresectable liver metastases refractory to standard of care therapies</li> <li>• Primary site: CRC (40%), NET (29%), Other (31%; incl. ICC)</li> <li>• Median age: 66 yr</li> <li>• ECOG PS ≤1 (96%; 0: 52%; 1: 44%)</li> <li>• Extrahepatic metastases (35%)</li> <li>• Bilobar (77%) and multifocal (89%) disease</li> <li>• Tumour burden ≤25% (65%)</li> <li>• Median <sup>90</sup>Y dose: 114.3, 115, and 115.7 Gy for CRC, NET, and Other, respectively</li> </ul>	<ul style="list-style-type: none"> <li>• ORR (RECIST): 5.2%, 20.9%, and 6.5% in CRC, NET, and Other, respectively</li> <li>• Median PFS: 2.9 and 2.8 mo in CRC and Other, respectively; not reached in NET (2-yr PFS: 67.4%)</li> <li>• Median survival: 8.8 and 10.4 mo in CRC and Other, respectively; not reached in NET (2-yr OS: 79.1%)</li> </ul>	<ul style="list-style-type: none"> <li>• Pain (12.8%), elevated alkaline phosphatase (8.1%) and bilirubin (5.3%), lymphopenia (4.1%), ascites (3.4%), vomiting (3.4%)</li> </ul>

4. Benson AB, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer* 2013;49:3122-3130.

# Glass Y90 Microspheres for Liver Metastases from CRC: Summary Phase II trails

No. of patients <sup>1-5</sup>	Predominant population studied <sup>1-5</sup>	Outcomes	Safety <sup>1-3,5</sup>
425	<ul style="list-style-type: none"> <li>• Unresectable liver metastases from CRC refractory to standard of care therapies</li> <li>• &gt;60 yr</li> <li>• ECOG PS ≤1 (89–96%; 0: 52–70%)</li> <li>• Extrahepatic metastases (35–78%)</li> <li>• Bilobar disease (77–83%)</li> <li>• Tumour burden ≤25% (65–81%)</li> <li>• Median <sup>90</sup>Y dose: 112.8–156 Gy</li> </ul>	<ul style="list-style-type: none"> <li>• ORR (WHO): 35–43%<sup>1-3</sup></li> <li>• ORR (PET): 73–90%<sup>1-3</sup></li> <li>• Median survival: 8.8–15.2 mo<sup>1-5</sup></li> <li>• ORR (RECIST): 5.2%<sup>4</sup></li> <li>• Median TTP: 15.4 mo<sup>4</sup></li> <li>• Median TTHP: 15.4 mo<sup>4</sup></li> <li>• Median PFS: 2.9 mo<sup>4</sup></li> <li>• 1- and 2-yr OS: 47.8% and 30.9%<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Fatigue (48–61%), abdominal pain (19–26%), and nausea (15–23%)</li> </ul>

1. Lewandowski RJ, Thurston KG, Goin JE, et al. 90Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135-150 Gy as measured by [18F]fluorodeoxyglucose positron emission tomography and computed tomographic imaging. *J Vasc Interv Radiol* 2005;16:1641-1651.
2. Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. *Radiology* 2008;247:507-515.
3. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer* 2009;115:1849-1858.
4. Benson AB, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer* 2013;49:3122-3130.
5. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging*. 2014;41:1861-1869.

# Resin Y90 Microspheres for Liver Metastases from CRC: Summary (Phase III/case control)

No. of patients <sup>6-9</sup>	Predominant population studied <sup>6-9</sup>	Outcomes	Safety <sup>6-9</sup>
240	<ul style="list-style-type: none"> <li>• Unresectable, chemorefractory liver metastases from CRC</li> <li>• &gt;60 yr</li> <li>• ECOG PS 0 (71–83%)</li> <li>• Extrahepatic metastases (22–48.3%)</li> <li>• Bilobar disease (70–90%)</li> <li>• Tumour burden ≤25% (40–56%)</li> <li>• Median <sup>90</sup>Y activity: 1.7–1.81 GBq</li> </ul>	<ul style="list-style-type: none"> <li>• ORR (RECIST): 9.5–41.4%<sup>6,8-9</sup></li> <li>• Median survival: 7.9–12.6 mo<sup>6-9</sup></li> <li>• 1-yr OS: 24–50.4%<sup>6,9</sup></li> <li>• Median TTP: 3.7–4.5 mo<sup>6,8</sup></li> <li>• Median TTHP: 5.5 mo<sup>8</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Fatigue, abdominal pain, and nausea</li> </ul>

6. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. *Br J Cancer* 2010;103:324-331.
7. Evans KA, Richardson MG, Pavlakis N, et al. Survival outcomes of a salvage patient population after radioembolization of hepatic metastases with yttrium-90 microspheres. *J Vasc Interv Radiol* 2010;21:1521-1526.
8. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 2010;28:3687-3694.
9. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012;35:1066-1073.

# TheraSphere<sup>®</sup> trials

Name	Disease	Comparison	Comment
EPOCH	2nd line Ca Colon	Second line chemo +/- SIRT	Open
STOPHCC	Unresectable HCC	Kinase inhibitor +/- SIRT	Open
Yes-P	Unresectable HCC with PVT	Kinase inhibitor +/- SIRT	Open

# Comparison

Factor	Y-90 SIR-Spheres®	Y-90 TheraSphere®
Effect	Radio-embolic	Radiation
Number of particles	+++++	+
Calculation of activity	Based on patient size (BSA)	Based on target dosimetry
Activity given	1-3BGq	2-6GBq
Administration time	45-90 minutes	10 minutes
Bilobar treatment	1-2 administrations	2 administrations
Side effects	Liver pain, low grade fever abdominal pain, nausea, jaundice	Liver pain, nausea, jaundice abdominal pain,

# Guidelines

- Procedural guidelines
- EANM revised 2011
- Based on safe practice
- Who to treat
  - Liver mets
  - Unresectable
  - >95% of tumour load
- Reduce lung radiation dose <30Gy

# Guidelines

- Clinical
- NICE (UK) 2013 to be considered in CRC mets and Ca cholangio: HCC trials only
- ESMO 2014 SIRT can be considered in patients with unresectable liver mets failing chemo (level IVB)
- ENETS, NANETS AUSNETS consider in liver mets of NETs

# Conclusions

- SIRT useful in mets in the liver
- Possible to use in HCC
- Needs good teams to work