

Radioactive Microsphere Therapy of Hepatic Neoplasm[©]

Warren H. Moore, M.D.
St. Luke's Episcopal Hospital

What is Nuclear Medicine?

Traditionally, Nuclear Medicine is the specialty of medicine which uses non-sealed sources of radioactivity for the diagnosis and treatment of disease.

What is a Non-Sealed Source of Radiation?

Official Definition: ...

Practical Definition: A source of radiation, other than external beam irradiation, which, once administered, can not be removed from the patient.

Who decides what is a sealed source of radiation (a “device”) vs. what is a non-sealed source (a “drug,” “radiopharmaceutical,” or “biological”)?

Officially: The FDA

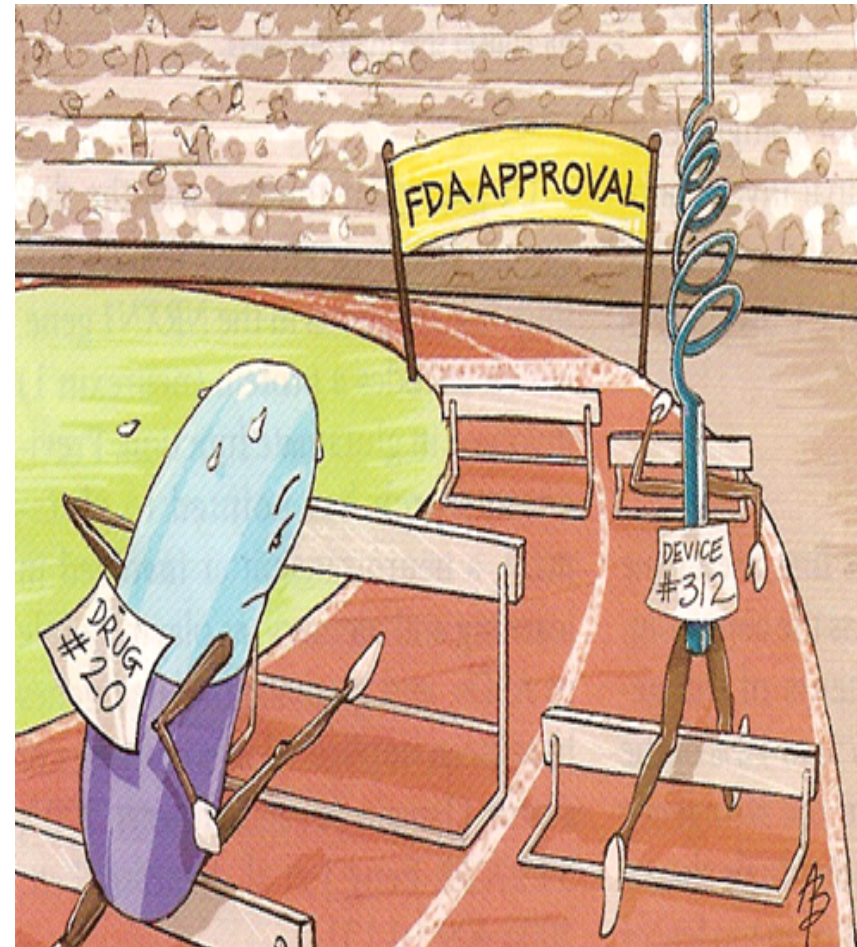
Practically: The manufacturer has a great influence on the decision.

Is a Y-90 microsphere a drug or a device? Is it a sealed or a non-sealed RAM?

- Tc-99m MAA
 - Mostly gamma emitter
 - Diagnostic intent
 - Several hundred thousand particles
 - Human albumin
 - 20-90 micron
 - Intravenous injection
 - No realistic way to retrieve particles
 - Particles stay in the body until metabolized
- Y-90 microspheres
 - Beta emitter
 - Therapeutic intent
 - Millions of particles
 - Glass or resin
 - 20-60 microns
 - Intraarterial injection
 - No realistic way to retrieve particles
 - Particles stay in the body permanently unless organ removed at surgery

Is a Y-90 microsphere a device or a drug? Is it a sealed or a non-sealed RAM?

- This is what the manufacturers knew.



JAMA 297:1304, 2007

SIRT

**Selective
Internal
Radiation
Therapy**

(SIRTeX Medical®)



Regulatory Requirements

- Y-90 microspheres must be used in accordance with US NRC and/or State RAM requirements
- 10 CFR Part 35.1000 (Other Medical Uses of Byproduct Material)
- Authorized User (AU)
 - Radiation Oncology
 - Nuclear Medicine
 - Interventional Radiology

Why Yttrium-90?

Physical properties are:

- **Pure beta** emitter
- Half Life = **64.1 hours**
- Energy of the beta particles:
 - Maximum = **2.27 MeV**
 - Mean = **0.93 MeV**
- **Range:**
 - Maximum in air = 9621 mm
 - Mean in air = 3724 mm**

 - Maximum in tissue = 11 mm
 - Mean in tissue = 2.5 mm**

Currently available commercial forms of
Yttrium-90 microspheres:

1. SIR-Spheres®
2. TheraSpheres®

Y-90 Microspheres Compared

Parameter	Glass (TheraSpheres)	Resin (Sir-Spheres)
Size	20-30 μm	20-60 μm
Isotope	Yttrium-90 in glass matrix	Yttrium-90 on resin surface
Specific Gravity	Higher	Lower
Activity/sphere (at calibration)	2500 Bq	50 Bq
# of dose sizes	6 (3,5,7,10,15,20 GBq)	1 (3 GBq)
# spheres/dose	1.2-8 Million	40-80 Million
# spheres/3GBq dose	1.2 Million	40-80 Million
US – FDA Approval	HCC	CRC metastases with FUDR pump

US Regulatory Status

- **SIR-Sphere: NDA**
- **TheraSphere designated as Humanitarian Use Device (HUD) (not NDA)**
 - **Legally marketed under Humanitarian Device Exemption (HDE)**
 - “Demonstrated safety and probable clinical benefit”
 - **HDE Requirements:**
 - IRB oversight and approval required
 - Use within approved labeling does not constitute research or investigational use

TheraSphere/Yttrium-90 Formulation

- Yttrium-89 oxide powder (yttrium is part of glass formulation)
- Molten glass made into microspheres (25 μm)
- Reactor activation:
 - Y-89 becomes Yttrium-90 (one week)
 - Byproducts from reactor activation: Eu-152, 154
- Benefits:
 - Yttrium-90 is an integral part of glass, which enables:
 - higher specific activity with minimal particles
 - no Y-90 leaching from the surface

- Microspheres are **intended for use on the day of calibration**. At the date and time of calibration, the activity in the vial matches the activity printed on the label (**3GBq^{+/-10%}**). The microspheres may be used for **up to 24 hours after calibration**.



Calibration Time

SIR-Spheres are typically manufactured about 48 hours prior to the treatment or **calibration date** to allow time for **shipping**. The calibration time also serves as a lockout time, before which the microspheres cannot be implanted. **The time from shipping to calibration provides a window for product recall.** The calibration time, date and reference time is on the attached label.



Calibration Time

- Beyond 24 hours after calibration, the number of microspheres required to provide sufficient activity increases by at least 30% and this may exceed the vascular capacity of the tumors in some patients (primarily with Sir-Spheres, less so with TheraSpheres).

Radiofrequency Ablation¹

- Accepted as best therapeutic choice for nonsurgical patients with early stage HCC
- Patient selection:
 - Single tumor < 5 cm, or < 3 nodules smaller than 3 cm each
 - No vascular invasion
 - No extrahepatic spread
 - Performance status of 0
 - Liver cirrhosis in Child-Pugh class A or B
- Considerations for use:
 - Avoid lesions located near gastrointestinal tract
 - Lesions located near gallbladder are at risk to injury of biliary tract
- Most common complications:
 - Intraperitoneal bleeding, hepatic abscess, bile duct injury, hepatic decompensation, and grounding pad burns

¹Lencioni, R. et al. *Techniques in Vascular and Interventional Radiology*. 2006;38-46

Systemic Chemotherapy - Sorafenib¹

Parameter	Sorafenib	Placebo
Patient selection	Child A/B = 284/14 BCLC B/C = 54/244	Child A/B = 297/6 BCLC B/C = 51/252
<u>Median overall survival</u>	10.7 months	7.9 months
Median time to symptomatic progression	4.1 months	4.9 months
Median time to radiologic progression	5.5 months	2.8 months
Tumor response (RECIST)	211 (71%) SD; 7 (2%) had PR; 0 CR	204 (67%) SD; 2 (1%) had PR; 0 CR
AE	80%	52%
SAE	52%	54%
Rate of Discontinuation due to AE	38%	37%
Dose Interruption due to AE	44%	30%

¹Llovet, JM. et al. *N Engl J Med* 2008;359:378-90

Particle Therapy

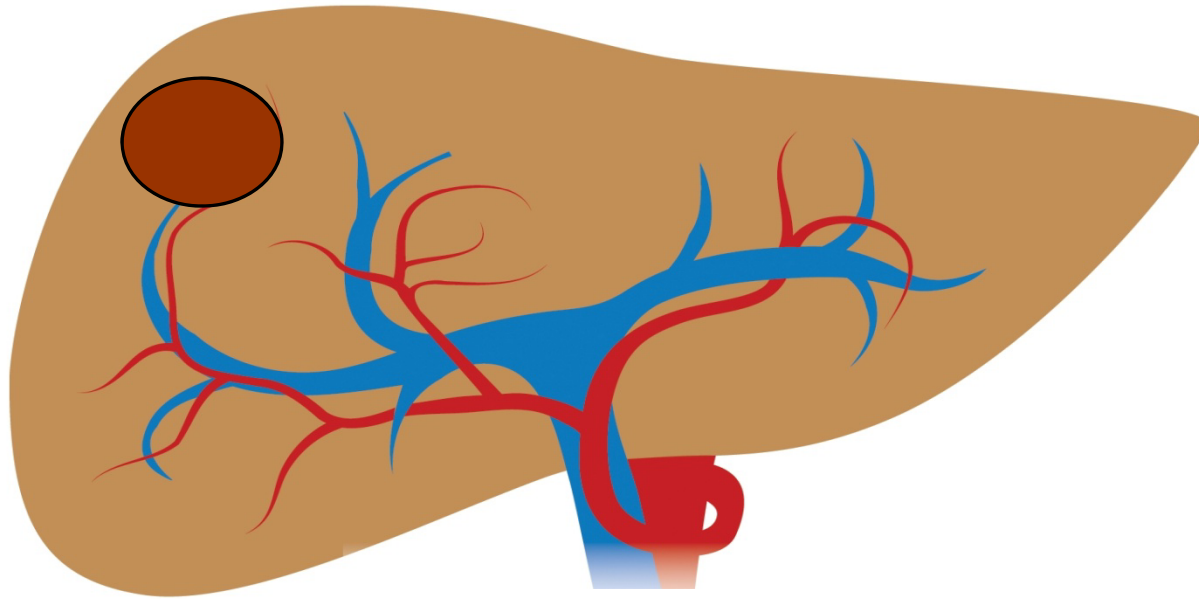
Parameter	Y-90 Glass Microsphere (TheraSphere)	Transarterial Chemoembolization (TACE)	Drug Eluting Beads (DEB – DC Bead)
Particle Size ^{1,2}	25µm	300 - 700 µm	100 - 700 µm
Mode of Action & No. of Treatment ^{1,2}	Beta Radiation Y-90) + minimal embolization (Avg 1.8/pt)	Chemotherapy + Embolization (variable cycles/pt)	Delayed chemo release + embolization (Treat every 3-4 wks)
Dosage	Standardized & Reproducible	Variable Regimens	Variable Regimens
Indications ^{1,2}	- Unresectable HCC (FDA)	- Not approved (FDA)	- Not approved (FDA)
Follow-up Tx Options	Any therapy (TACE/RFA/Y-90, etc.)	Limited options; must wait for recanalization	Limited options; must wait for recanalization

¹Salem et al. *JVIR (Part 1)* 2006;17(8):1251-1278

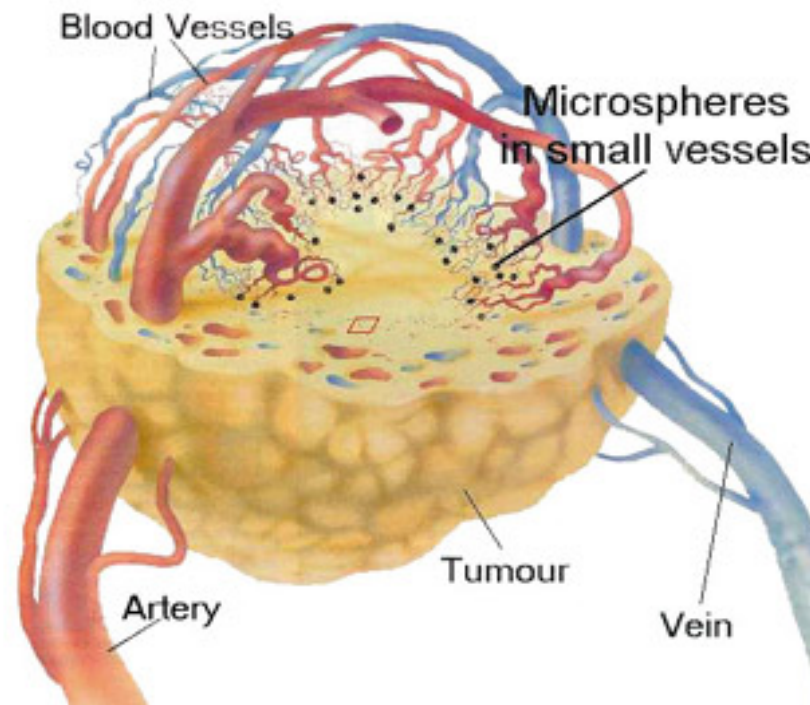
²www.Biocompatibles.com (accessed December 1 2008)

Vascular Delivery

Hypervascular Tumor (3:1) – preferentially delivered to tumor

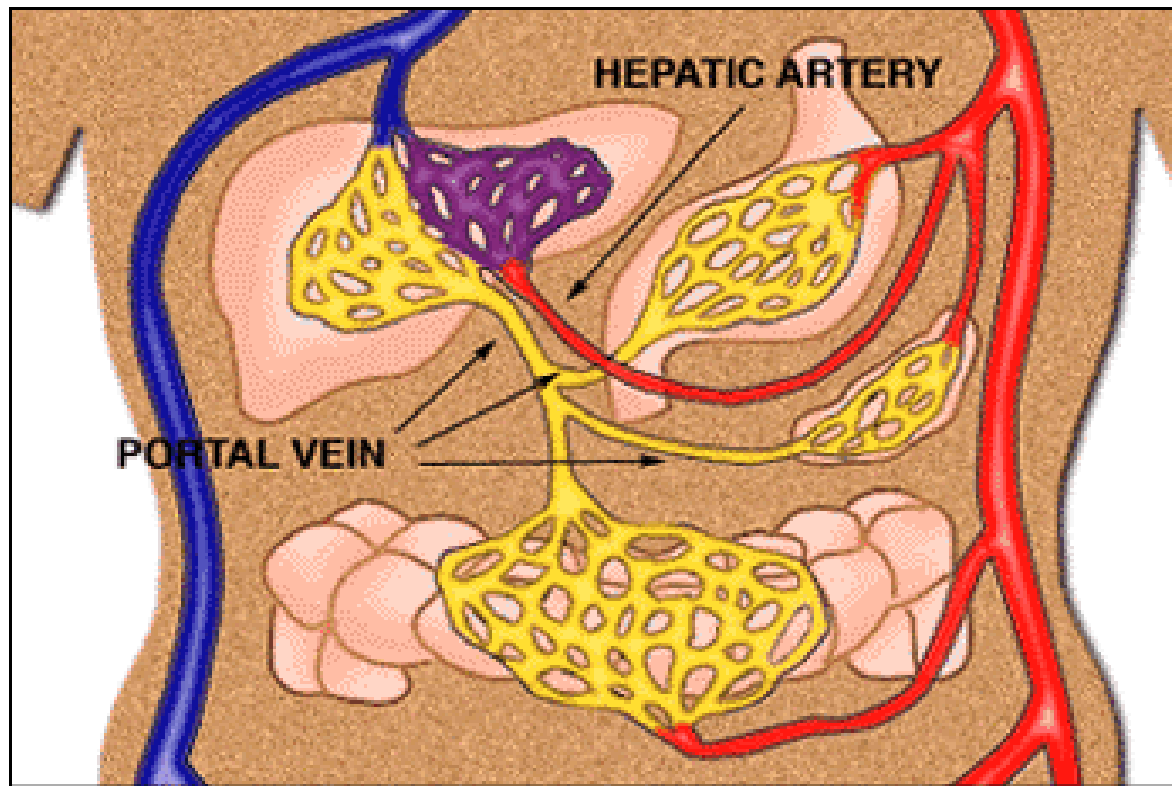


Radiolabeled Microspheres

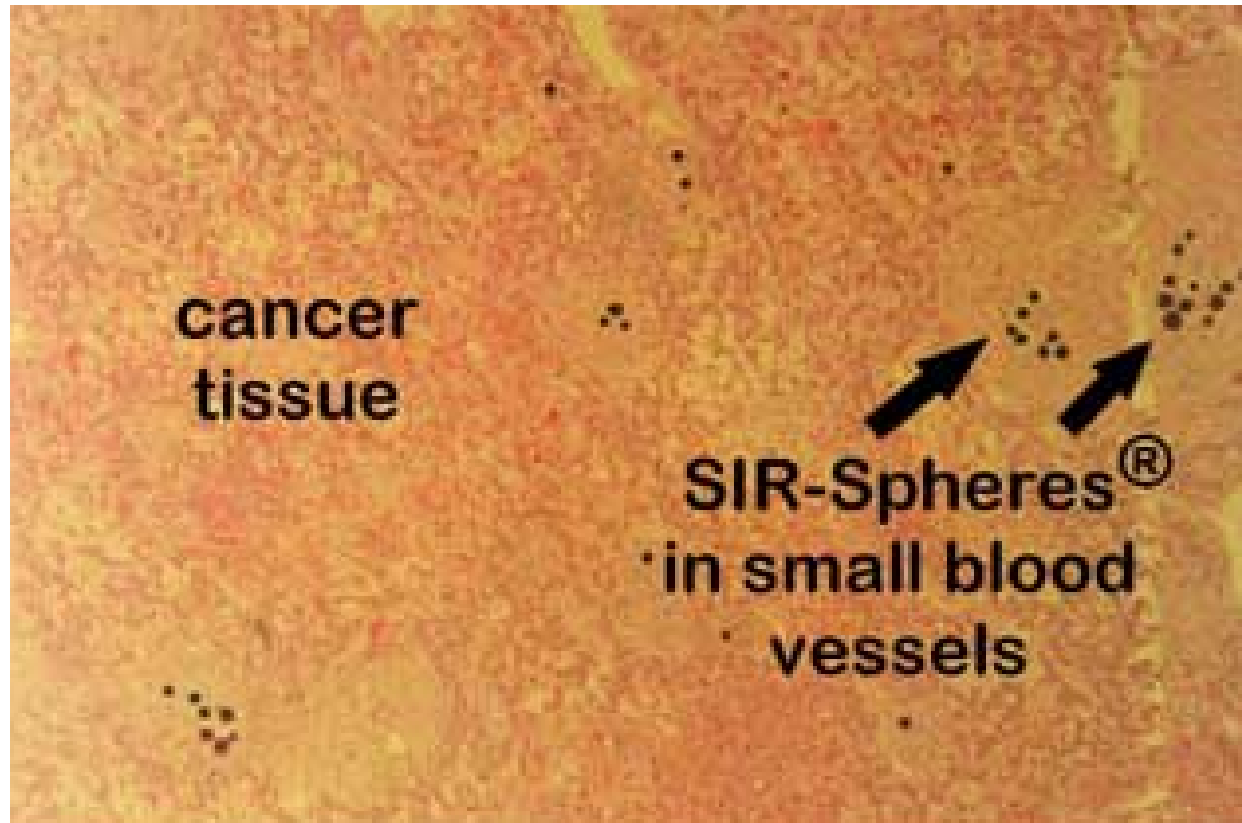


Does Size of the Microspheres Matter?

The **upper size limit allows** delivery to the tumors via the hepatic artery. The **lower size limit prevents** the microspheres passing from the arterial circulation through the tumor vasculature and into the **venous (and systemic)** circulation.



Radiolabeled Microspheres



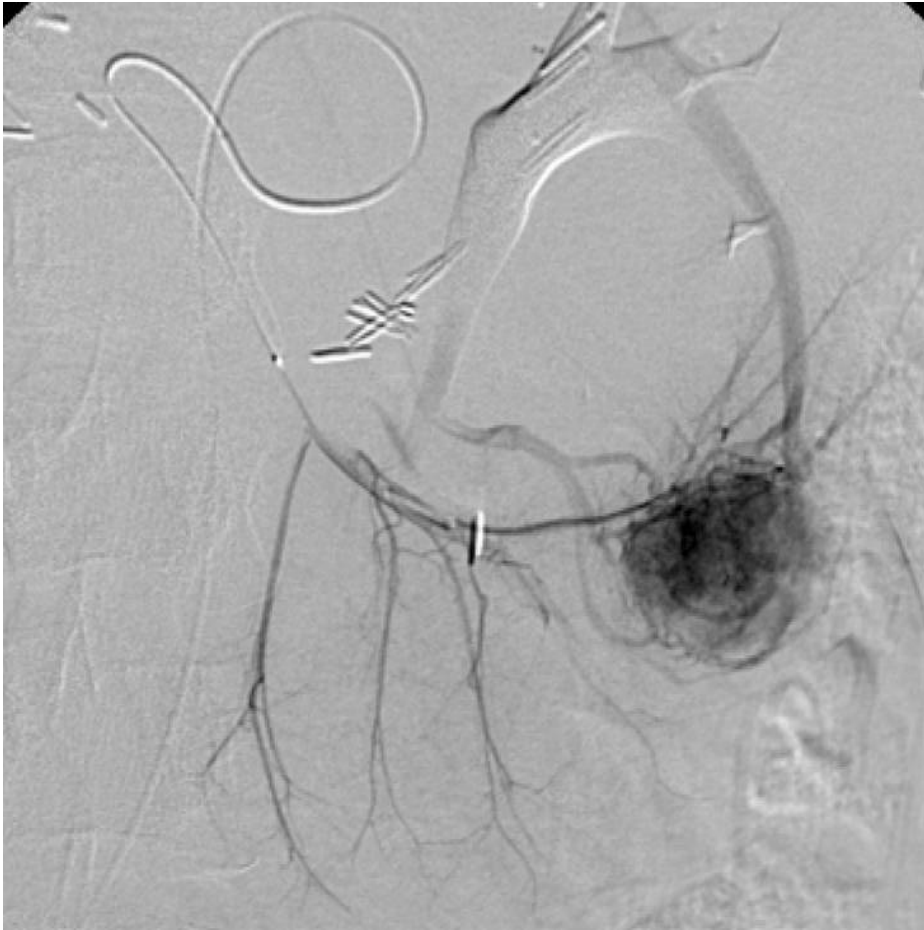
Microsphere Benefits Overview

Targeted Therapy: Sparing Healthy Tissue

- Low toxicities: well tolerated
- Outpatient procedure
- Minimal embolic syndrome
(TACE vs. microsphere)
- Promising survival data
- Post-microsphere patients eligible for further therapeutic options due to preserved liver vascularity

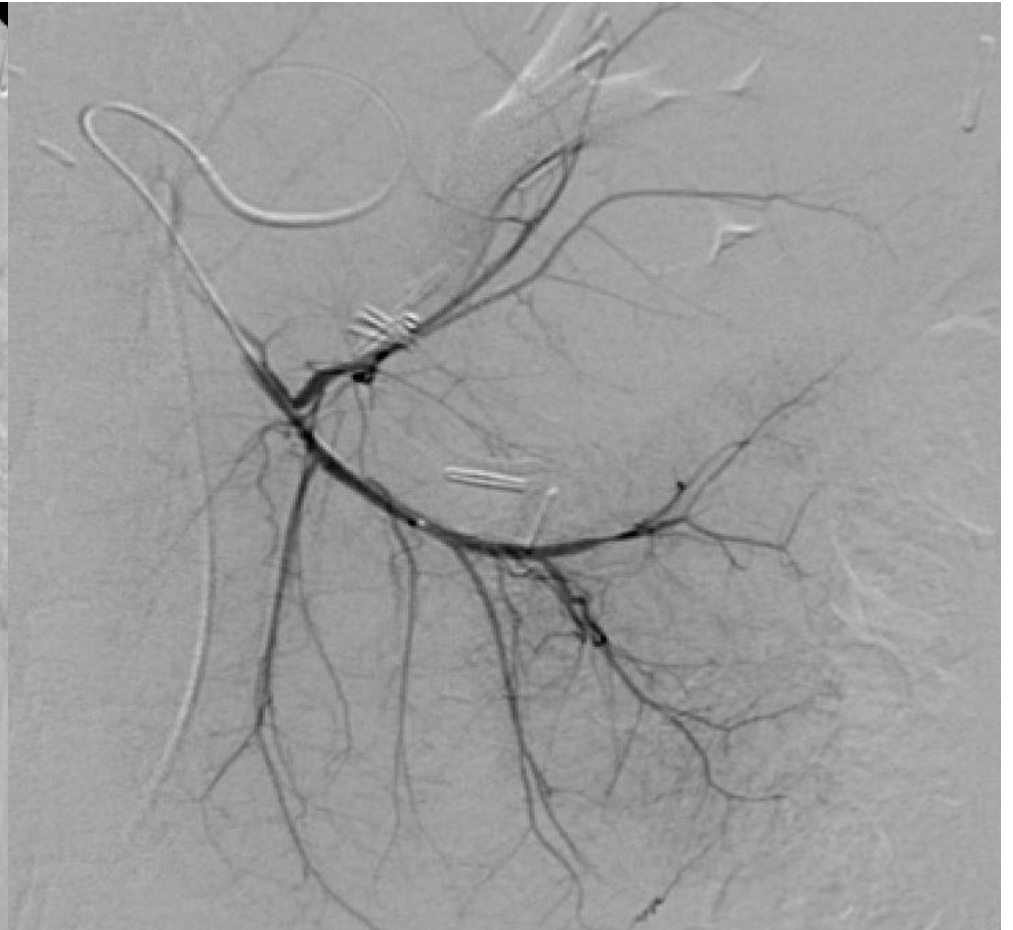


Tumor Vascularity



- Pretreatment angiogram demonstrating hepatic vein (hyperdynamic) flow

Atassi et al. Radiographics 2008;28 (1): 81-99



- 45 day post-treatment angiogram demonstrating elimination of tumor vascularity while preserving normal parenchymal flow

Addressing Common Adverse Events

- Fatigue
 - Usually lasts 10 – 12 days
 - Can be offset by Medrol dose pack
- Mild abdominal pain or discomfort
 - Bloating/nausea
 - Relieved by conservative measures
- Fever/Night Sweats
 - Bulky disease
 - Cytokine release from tumor necrosis
 - Rule-out other causes
 - Relieved by conservative measures

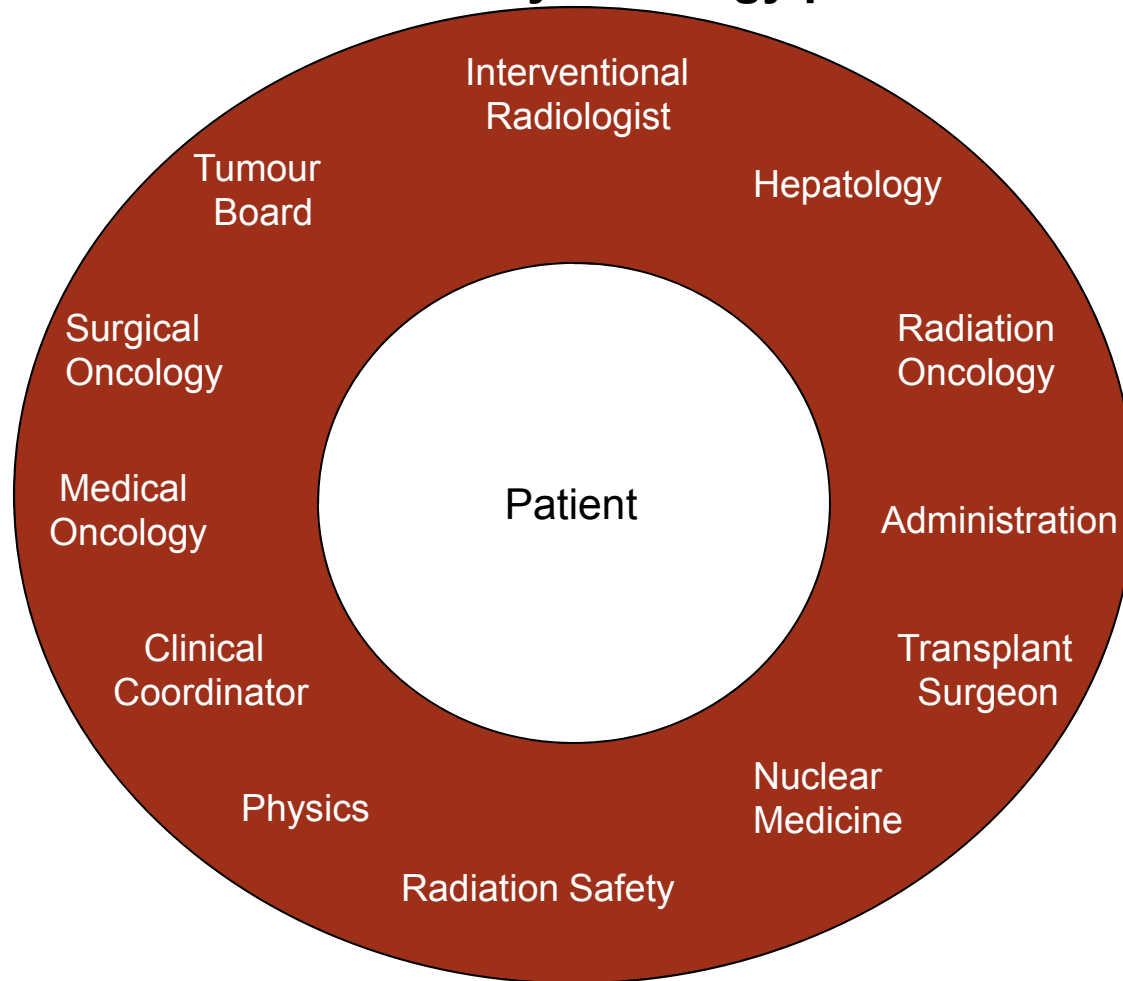
Radiolabeled Microspheres

- **Serious Side Effects**
 - Nausea/Vomiting
 - Abdominal Pain
- **Serious Distant Tissue Effects**
 - Pneumonitis due to intrahepatic shunting from hepatic arterial circulation to the hepatic venous system
 - Mucosal damage in stomach and gut due to GDA perfusion
 - Pancreatitis due to pancreatic arterial perfusion

Treatment Approach & Patient Selection

Multidisciplinary Team

Similar for many oncology patients



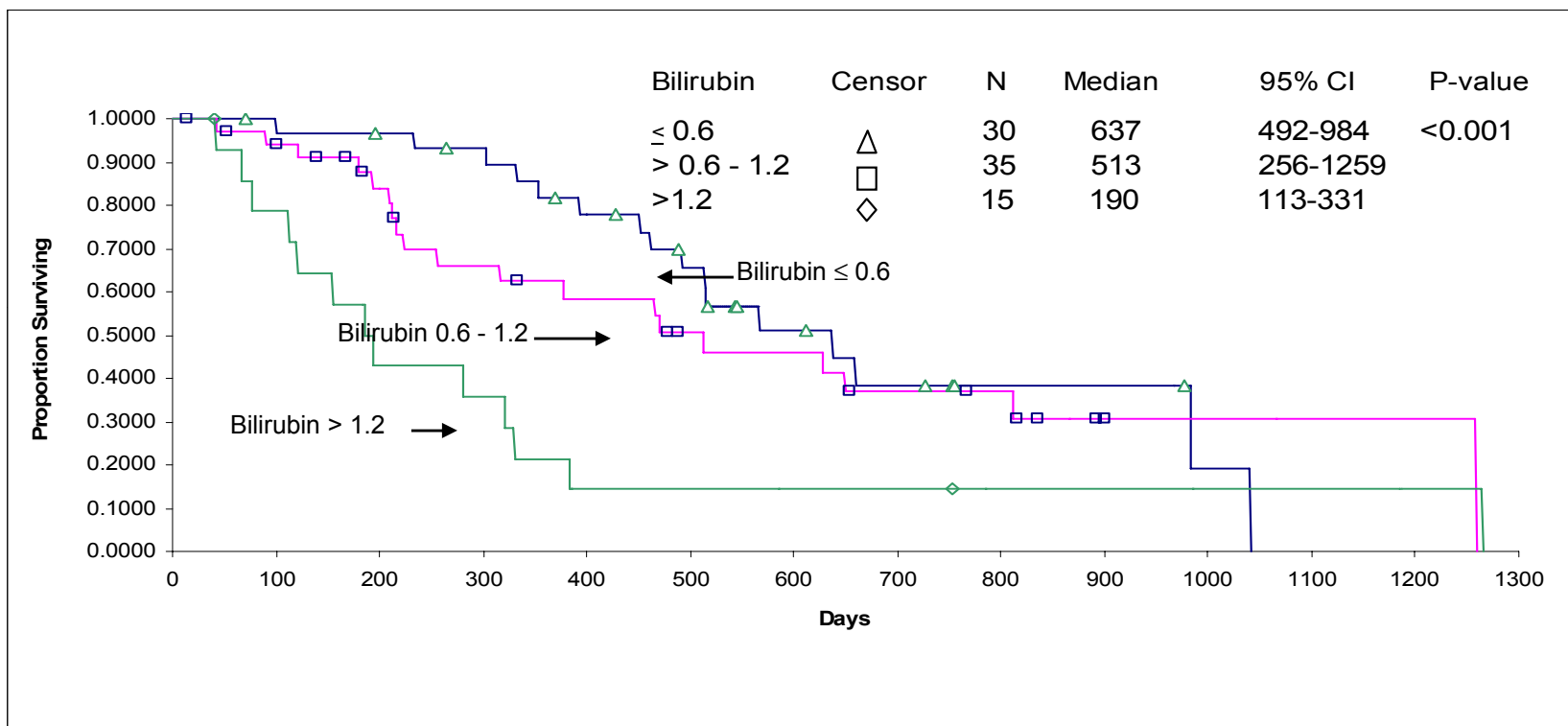
Patient Selection

The ideal candidate for microspheres presents with:

- **Non-infiltrative tumor type**
- **tumor nodules that are not too numerous to count**
- **AST/ALT < 5 x ULN**
- **Tumor volume \leq 50% and Albumin > 3 g/dL**
- **Bilirubin \leq 2 mg/dL**

Importance of Bilirubin in Patient Selection

(n = 80)

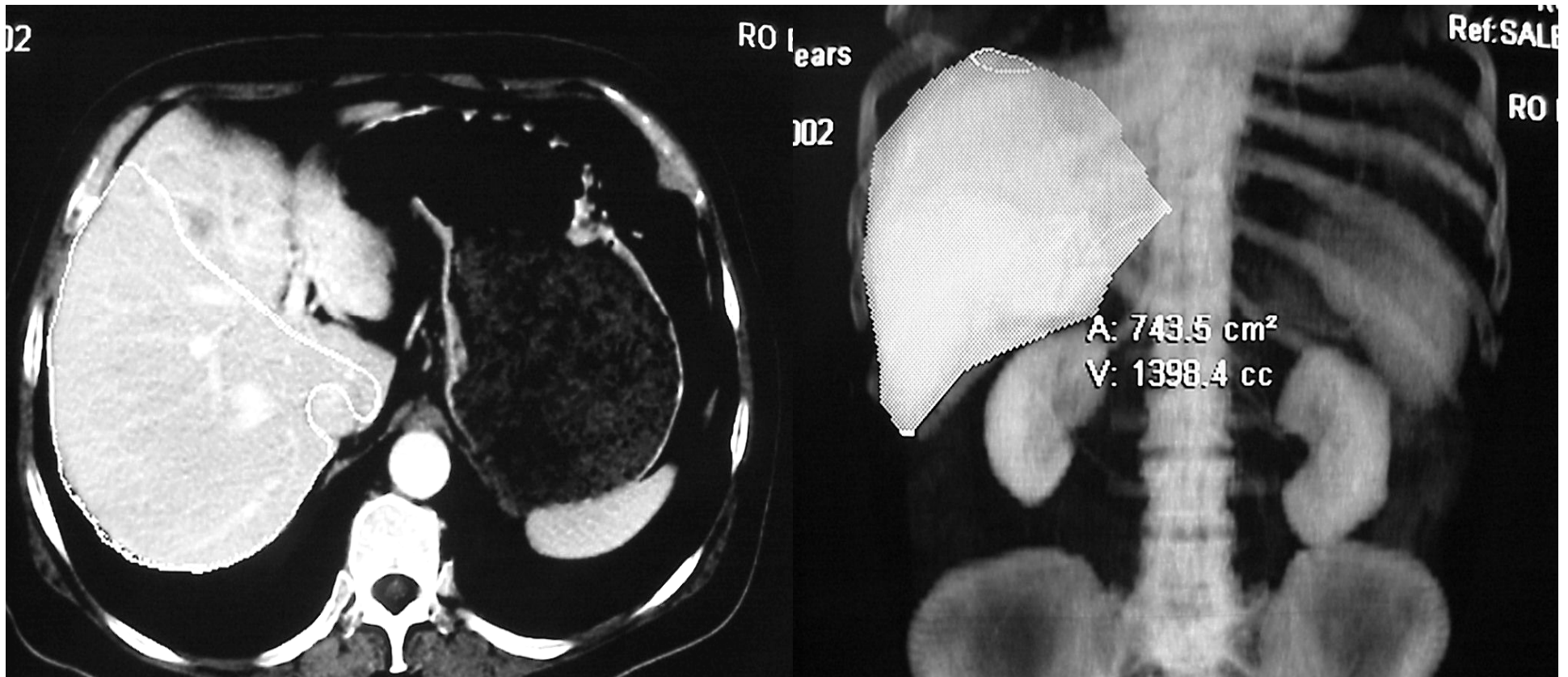


Patient Planning

TheraSphere Dosimetry Planning

- Obtain liver volume from CT scan / angiogram
- Perform Tc-99m MAA scan
- Determine required TheraSphere dose
(3, 5, 7, 10, 15 or 20 GBq)
- Based on:
 - optimal therapeutic dose
 - liver mass
 - physical decay of Y-90 and resulting activity at time of treatment
 - treatment time window
 - written directive

Volume analysis: CT Imaging



Pretreatment Angiogram & Tc-99m MAA Scan

- Hepatic angiogram with placement of intra-hepatic catheter to assess vasculature and microsphere delivery route
- Technetium-99m Macroaggregated Albumin (Tc-99m MAA) study to assess extrahepatic flow to GI tract and/or pulmonary shunting



Clinical Outcomes

Large Lesion



Large right lobe HCC

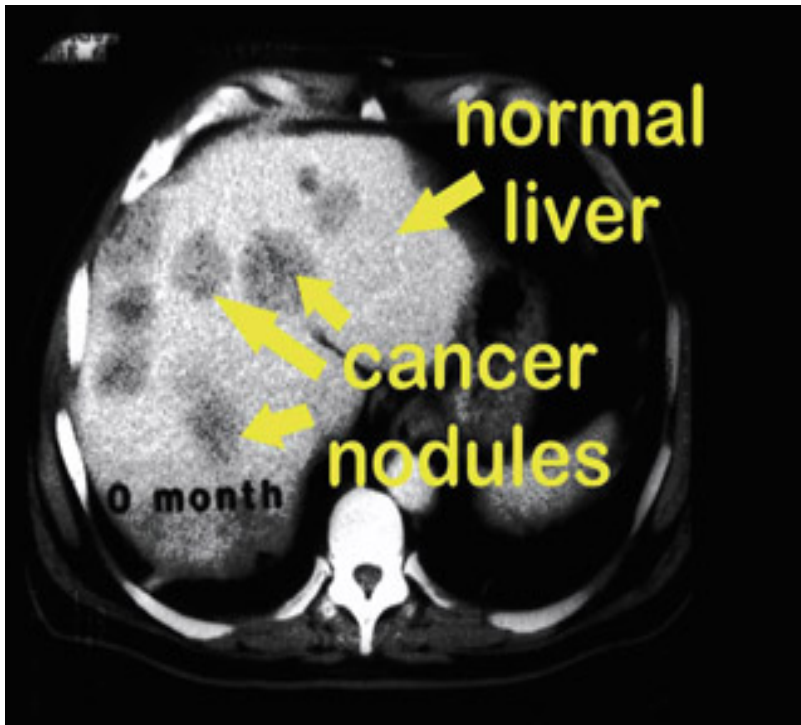
- Patient treated with 1 dose of TheraSphere

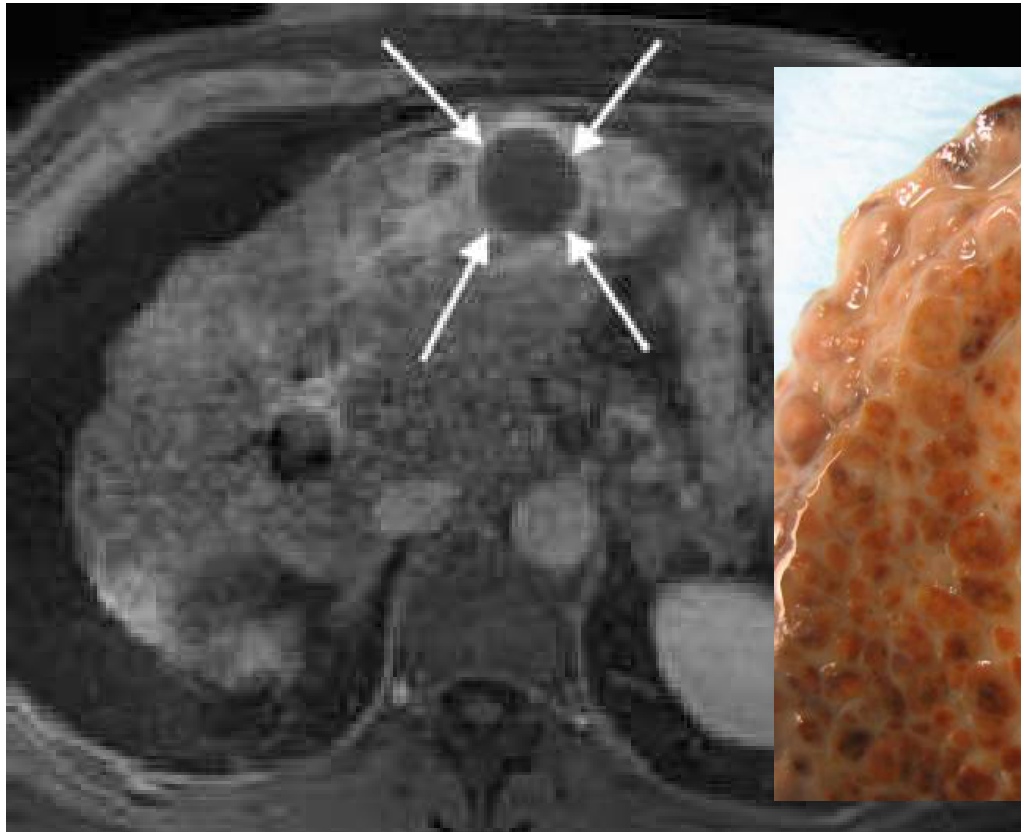
2 months post treatment

8 months post treatment

Images provided by Riad Salem, Interventional Radiologist, Northwestern University, Chicago, Illinois

Multiple Lesions





HCC post downstaging to transplantation

- Arrows point to enhancing capsule following treatment.

Explant demonstrates complete necrosis of the tumor (42 days post Tx).

Kulik, et al. Liver Transplantation 2005;11(9):1127-1131

Technical Issues

Patient Dose Calculation

Activity required to administer 150 Gy to the right lobe:

$$\begin{aligned} \text{Activity} &= \frac{[\text{Desired Dose (Gy)}] [\text{Liver Mass (kg)}]}{50 [1-F]} \\ \text{Required} &= \\ \text{(GBq)} & \end{aligned}$$

$$\text{Liver Mass} = 1301 \text{ cc} * 1.03 \text{ g/cc} * 1 \text{ kg}/1000\text{g} = 1.340 \text{ kg}$$

$$\begin{aligned} \text{Activity} &= \frac{[150\text{Gy}] [1.340 \text{ kg}]}{50 [1-F]} \\ \text{Required} &= \\ \text{(GBq)} & \\ &= 4.02 \text{ GBq} \end{aligned}$$

Dose Scheduling

	Delivered Dose for Ordered Activity (GBq) =					7
Time	Monday	Tuesday	Wednesday	Thursday	Friday	
8:00 AM	211	162	125	97	75	
12:00 PM	202	156	120	92	71	
4:00 PM	193	149	115	89	68	
8:00 PM	185	143	110	85	66	
	Delivered Dose for Ordered Activity (GBq) =					5
Time	Monday	Tuesday	Wednesday	Thursday	Friday	
8:00 AM	150	116	89	69	53	
12:00 PM	144	111	86	66	51	
4:00 PM	138	106	82	63	49	
8:00 PM	132	102	79	61	47	

Radiolabeled Microspheres

- Dose varies depending on
 - User philosophy
 - Tumor burden
 - Degree of hepatic-to-systemic shunting
- Maximum dose (SIR-Spheres[®]) in US is 3 GBq (81 mCi)
 - But rarely use more than 2 GBq (54 mCi)
- Doses of up to 8 GBq have been used, with significantly increased side effects

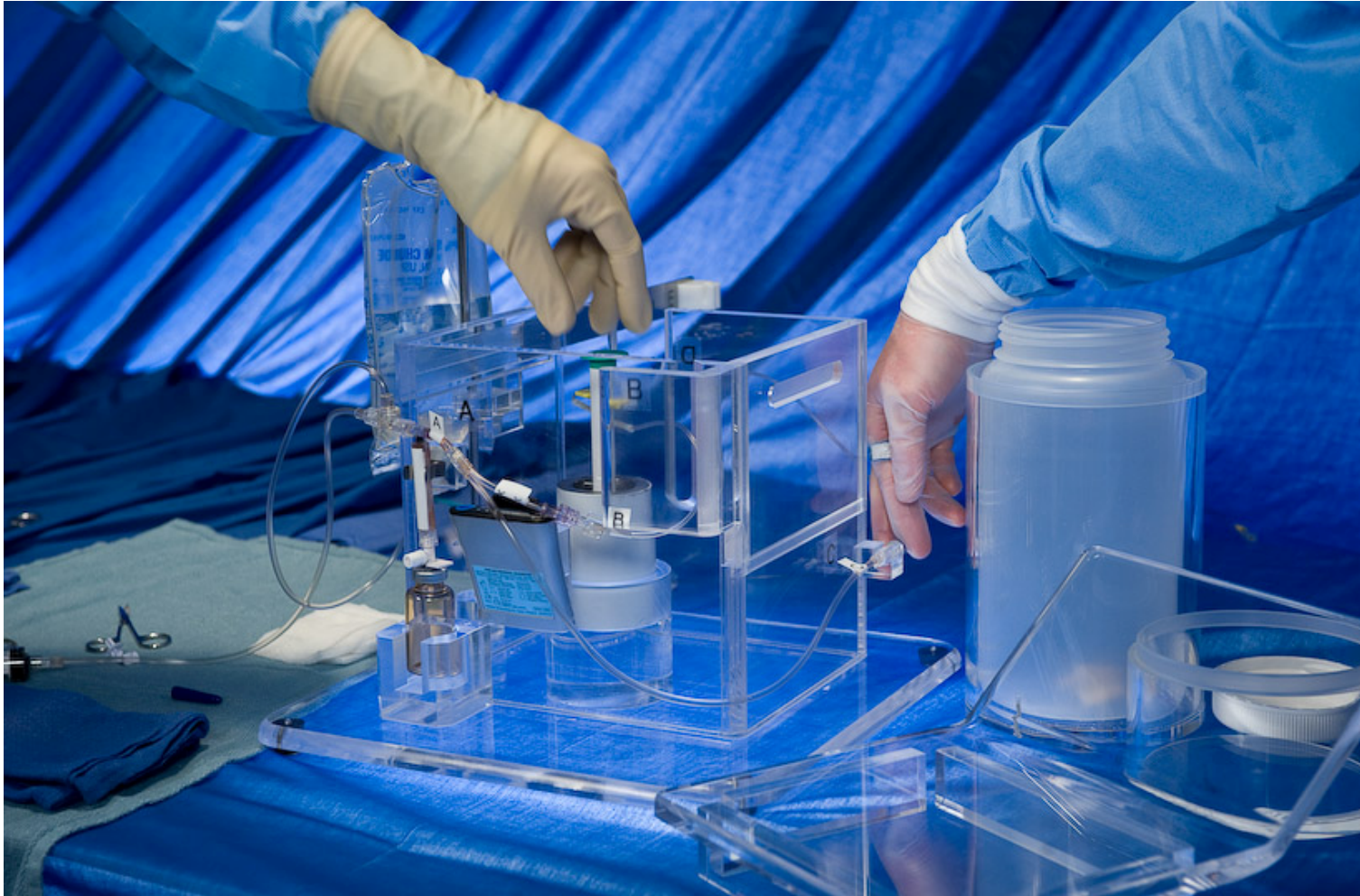
Activity Calculations



- The activity of the microspheres implanted will usually be in the range of **1.0-2.5 GBq**

Site Dose Measurement

- The use of a dose calibrator must follow manufacturer instructions, there must be a comprehensive program to evaluate geometry, repeatability, linearity, NIST Program
- The holder used has a very important effect on geometry and the accuracy of the activity measurement.
- Unique site factor determination



Radiation Safety

Monitoring should occur at two levels:

- the environment
- the staff.

Radiation Safety

- The treatment of patients using microspheres requires the **standard shielding**, protective clothing, gloves, radiation surveys, and training of personnel involved in the procedure as well as the **staff nurses**.

Radiation Safety

- Acceptable levels for the **environment** are established using a beta counter and **anything above background should be considered contaminated.**

Radiation Safe



- Items that may become **contaminated with Yttrium-90** must be bagged, labeled, and returned to the nuclear medicine/radiation therapy department or other designated areas to **decay for a period of ten half-lives** (? long-lived contaminants) i.e. until the measured activity does not exceed background levels.

Radiation Safety **Instructions** for the Patient

Instructions for the patient should be based on measured or typical exposure readings.

For example, for a **1.5 GBq** (40 mCi) dosage:
typical exposures have been:

surface = 1.0 mR/hr

1 meter = 0.1 mR/hr

Conclusions

Radiolabeled Microspheres

- According to FDA, these are devices
- Labeled with beta emitting Y-90
- TheraSpheres and SIR-Spheres differ by size, composition, and specific activity
- Only fully “approved” use is SirSpheres for colorectal cancer metastatic to liver
- Generally well tolerated but serious adverse effects of improper deposition
- Good clinical outcomes in difficult patient group
- Expensive, but cheaper than chemotherapy