

What is Nuclear Medicine?

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

Radiopharmaceuticals

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.

Radiopharmaceuticals

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

Officially: The FDA

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

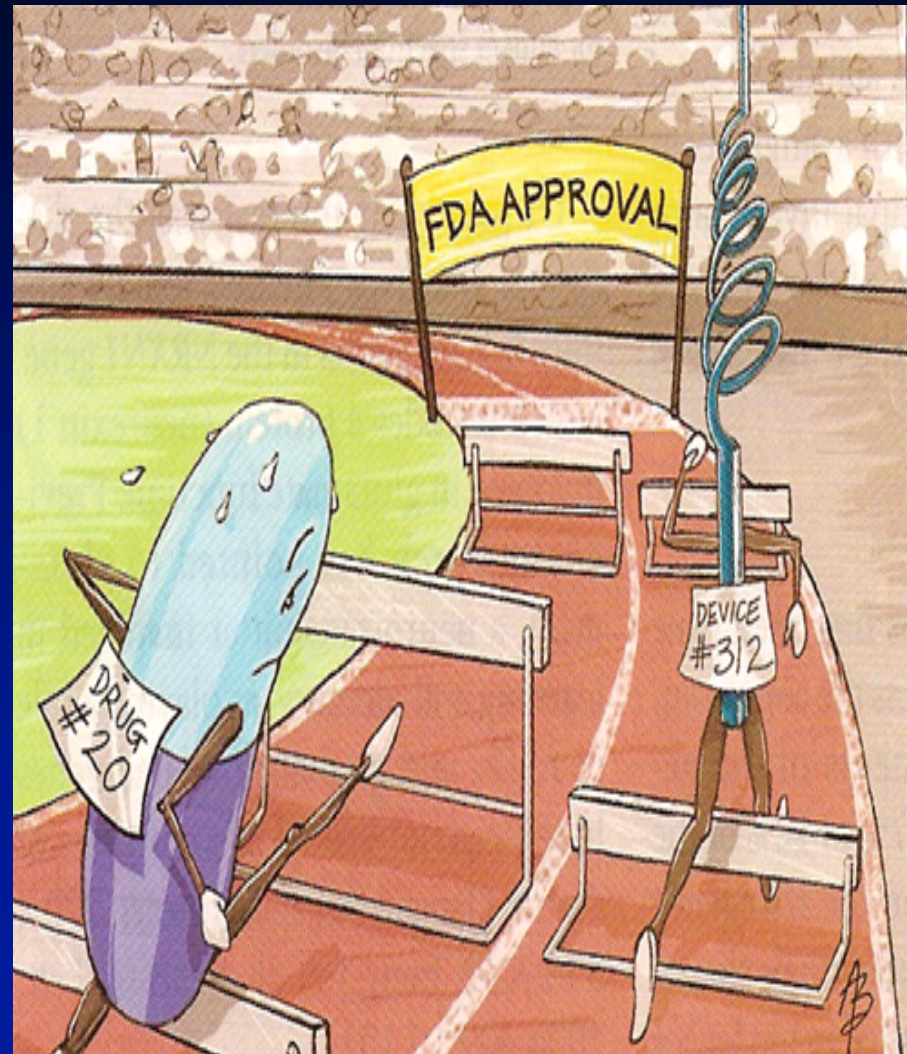
Radiopharmaceuticals

**What is a Non-Sealed Source of Radiation?
Why does it matter to us?**

- 1. Different agencies and routes of approval**

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

- ◆ **This is what the manufacturers knew.**

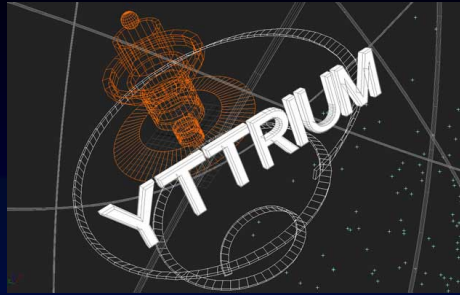


JAMA 297:1304, 2007

SIRT

Selective
Internal
Radiation
Therapy





Currently two commercial forms of **Yttrium-90 microspheres** are available:

1. **TheraSpheres®**
2. **SIR-Spheres®**



Y-90 Microspheres

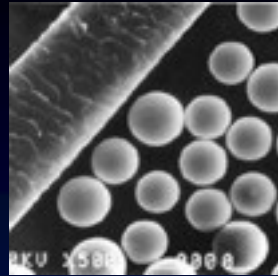
1. TheraSpheres[®]

glass, 25 μm , “Humanitarian Use”

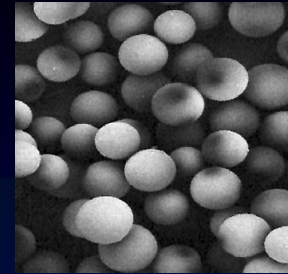
2. SIR-Spheres[®]

resin, 35 μm , full “approval”

Theraspheres



Microspheres

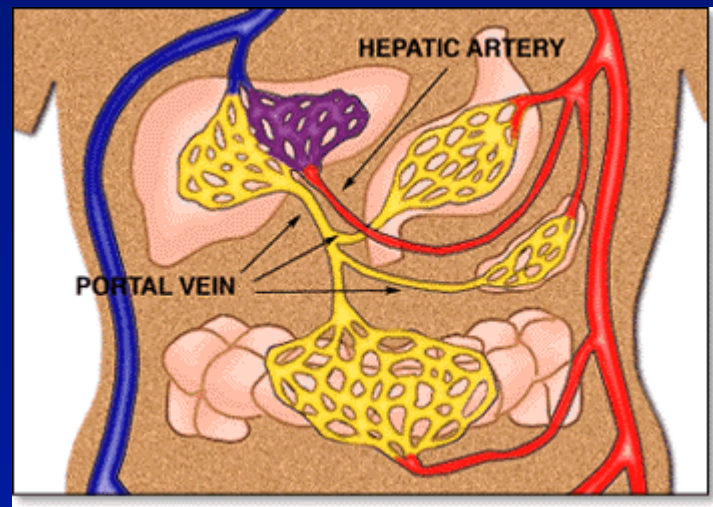


- ◆ While the commercial products use the **same radioisotope** and have the **same target dose** (≈ 100 Gy ($\approx 10,000$ rad)), they **differ** in microsphere **size** profile, base **material** (i.e. **resin versus glass**) and **size of commercially available doses**.
- ◆ These physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and theoretical dosimetry calculations.

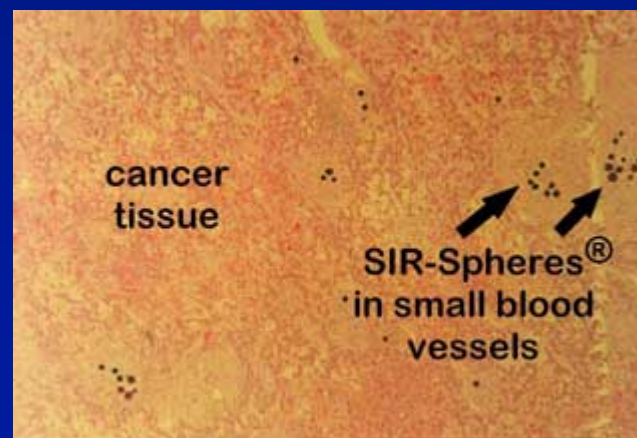
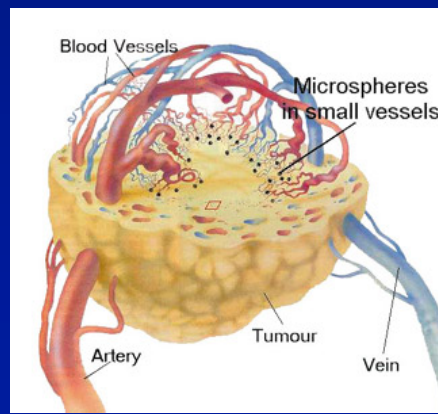
Physical Characteristics

- ◆ **Microspheres consist of biocompatible materials designed to be between 20-60 microns in diameter, containing Yttrium-90, a high-energy pure beta-emitting isotope with no primary gamma emission.**

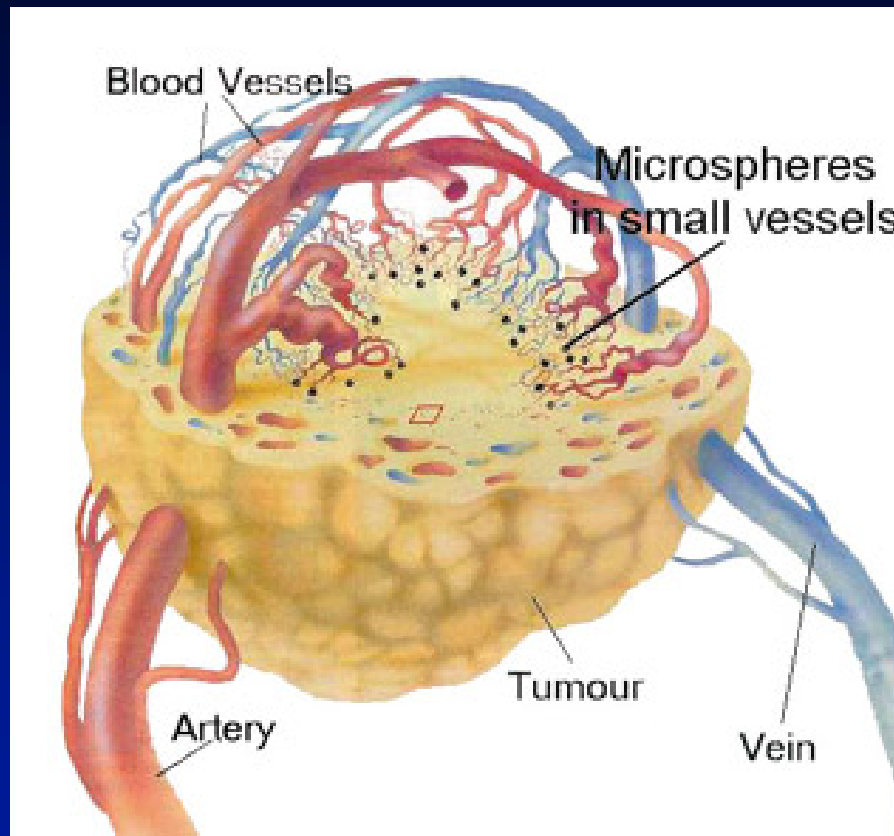
- ◆ The **upper size limit** of the microspheres allows delivery to the tumors via the hepatic artery. The **lower size limit prevents** the microspheres passing from the arterial circulation through the tumor vasculature and into the **venous (and systemic)** circulation.



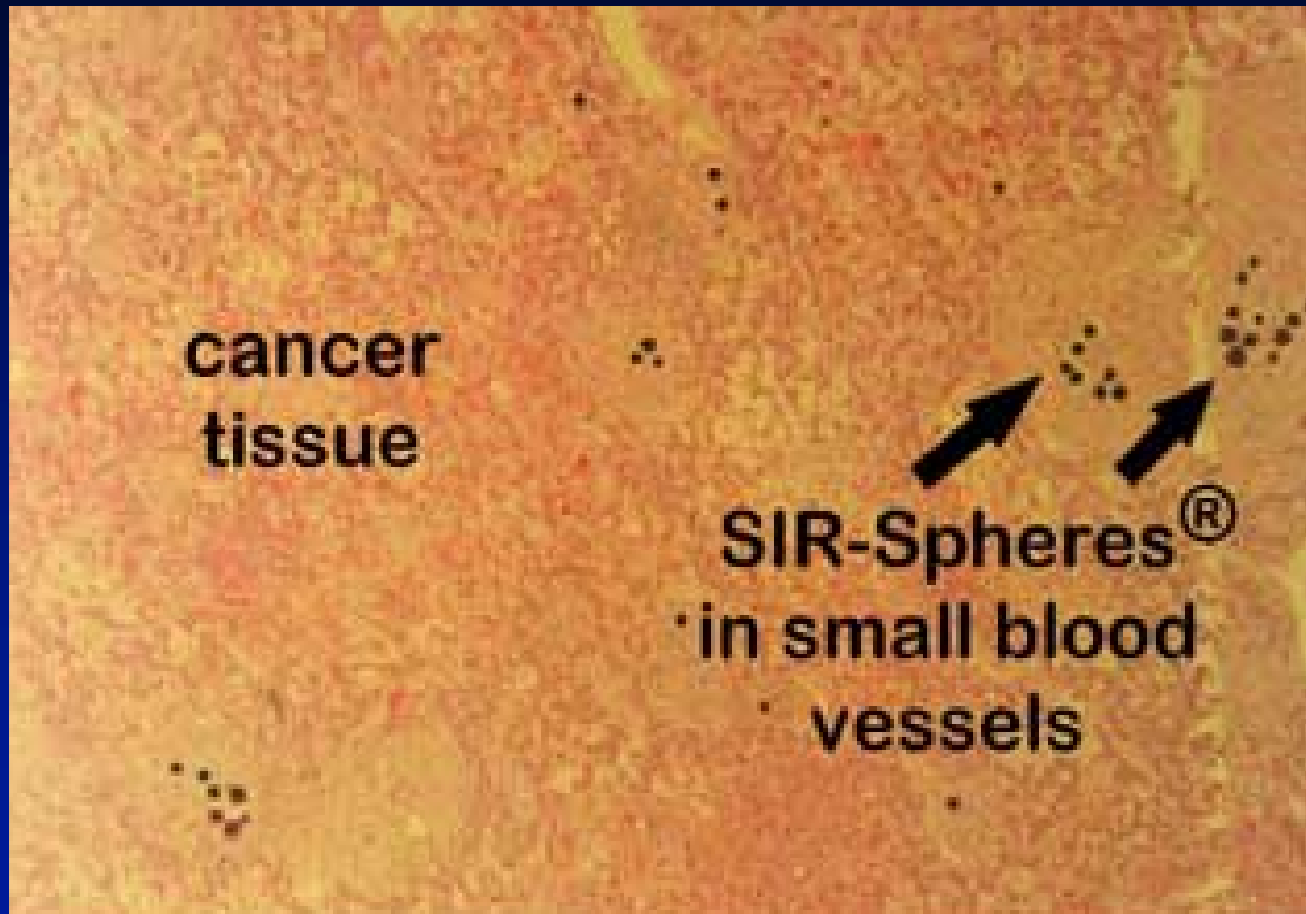
- ◆ The microspheres remain trapped within the vasculature of the tumors and deliver a radiation dose to the surrounding tissue. The **microspheres do not degrade and remain permanently implanted.** They are **not retrievable** unless the **tumor is resected** at a later stage.



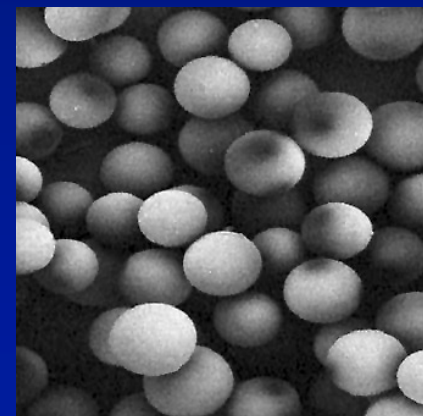
Radiolabeled Microspheres



Radiolabeled Microspheres



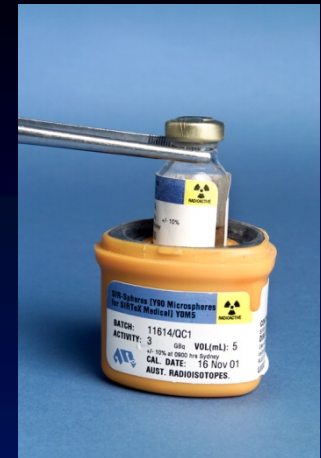
- ◆ **SIR-Spheres** microspheres are suspended in pyrogen free **water** for injection to a total of **5 ml per 3 GBq (81 mCi)**. This allows the activity required for implantation into individual patients to be **measured as a volume**.



Therasphere[®] Administration



- ◆ The (microsphere) **device** is supplied with a **calibration certificate** and decay graph to allow for estimation calculation of the remaining activity of the product on arrival. **This should be separately and independently verified.** The device consists of a **suspension** of microspheres in the water for injection. Each device is moist heat-sterilized and **single-use** only.



- ◆ The **activity** of the microspheres, **rather than their weight** or volume, determines the **number of micro-spheres delivered** to any individual patient. The total **radiation required** by a patient is **dependent on the extent of tumor tissue** and is at the discretion of the treating physician.

Yttrium-90 is a pure beta-emitting isotope

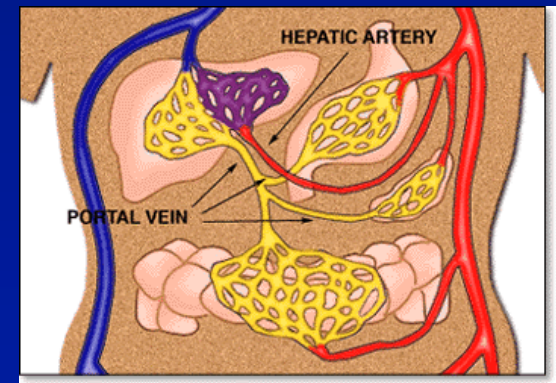
The properties are:

- ◆ 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**

- ◆ 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**.



- ◆ **Beyond 24 hours, the number of microspheres required to provide sufficient activity increases by approximately 30% and this may exceed the vascular capacity of the tumors in some patients.**



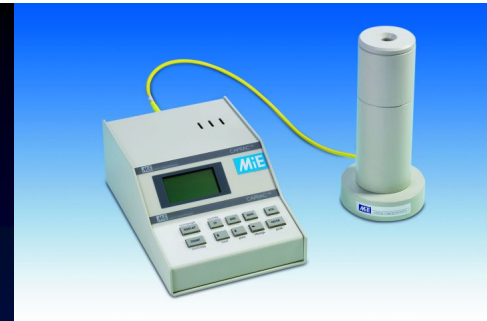


- ◆ **Microspheres are typically manufactured about 48 hours prior to the treatment or calibration date to allow time for **shipping**. The calibration time also serves as a lockout time, before which the microspheres cannot be implanted. **The time from shipping to calibration provides a window for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

Radiation Dosimetry

- ◆ **Point Source Beta Radiation** - There is **no simple way** to precisely know the radiation dose to tumors, normal liver or adjacent organs when microspheres are implanted. This is because Y-90 only emits pure beta radiation with limited penetration range in tissue. **Mathematical calculations** of the dose from a Y-90 point source of beta radiation show that the dose is largely confined to a distance of **2-3 mm from the point source**. The total dose at any particular position of interest in the implanted tissue can **theoretically** be found by **summing together the contributions from all of the individual point sources in the vicinity**.

Calibration Equipment



- ◆ The most common radioisotope calibrators in use are **well type ionization chambers**. The accuracy of measurement may be dependent upon the range of activity being measured. At the **manufacturer's suggested settings**, measurements up to 3 GBq are generally linear and consistent. If alternative settings are used and not recommended by the manufacturer, linearity and accuracy should be reconfirmed.

Activity Calculations



- ◆ The **activity** of the Yttrium-90 should be **determined by measurement** using an appropriate dose calibrator, such as an ion chamber, upon arrival or at the time of dose preparation. **Confirmation that the correct activity has been drawn from the vial should also be directly verified** by measurement, and the **residual syringe activity measured** and subtracted to determine the actual patient dosage.

Activity Calculations

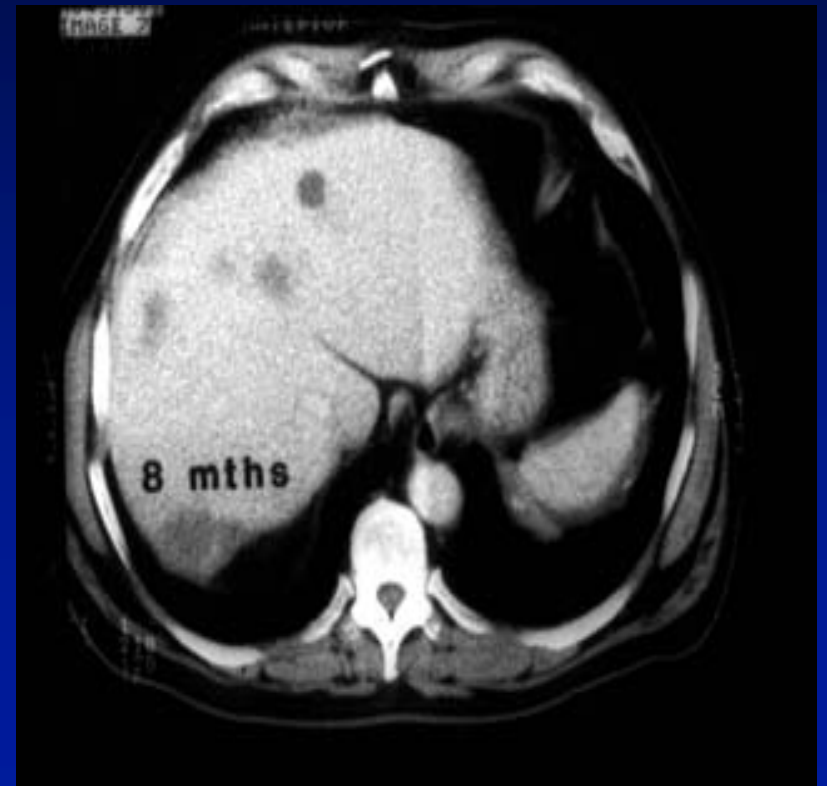
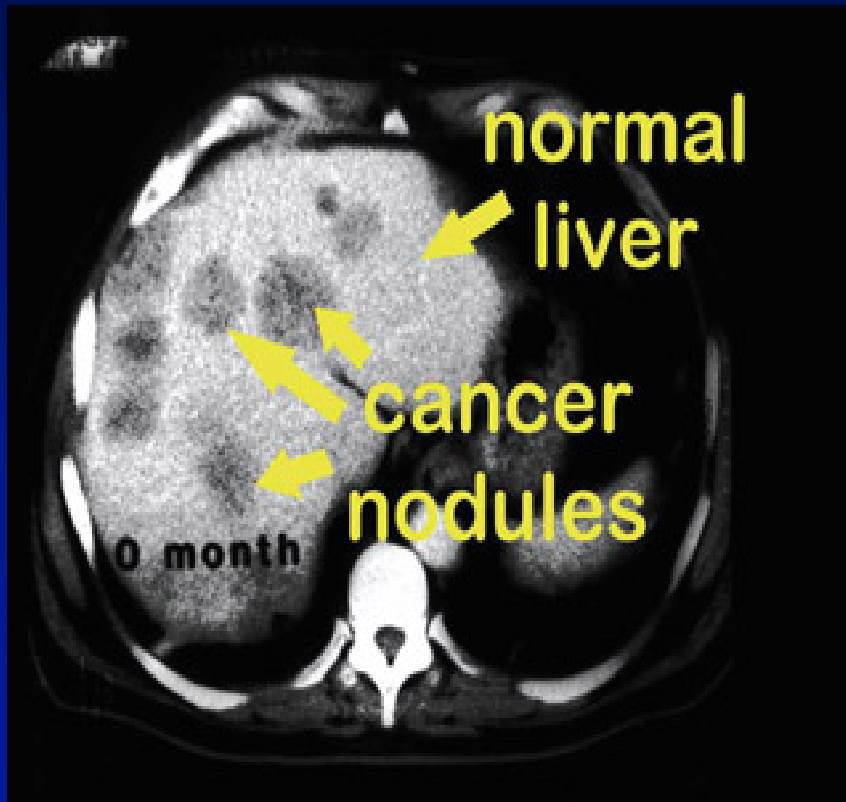


- ◆ Drawn doses must **allow for decay during the time between dose preparation and implantation.** The decay table supplied with the device can be used for his purpose. The activity of the microspheres implanted will usually be in the range of **1.0-2.5 GBq**

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

Therapeutic Y-90 Spheres



Radiolabeled Microspheres

◆ Side Effects

- ◆ Fatigue/malaise
- ◆ Fever
- ◆ Nausea/vomiting
- ◆ Acute abdominal pain
- ◆ Radiation Hepatitis
- ◆ Embolic Syndrome (as for nonradiolabeled therapeutic embolization)
- ◆ Distant Tissue Effects

Radiolabeled Microspheres

- ◆ **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**

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

Monitoring should occur at two levels:

- ◆ the environment
- ◆ the staff.

Radiation Safety

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

Radiation Safety



- ◆ 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

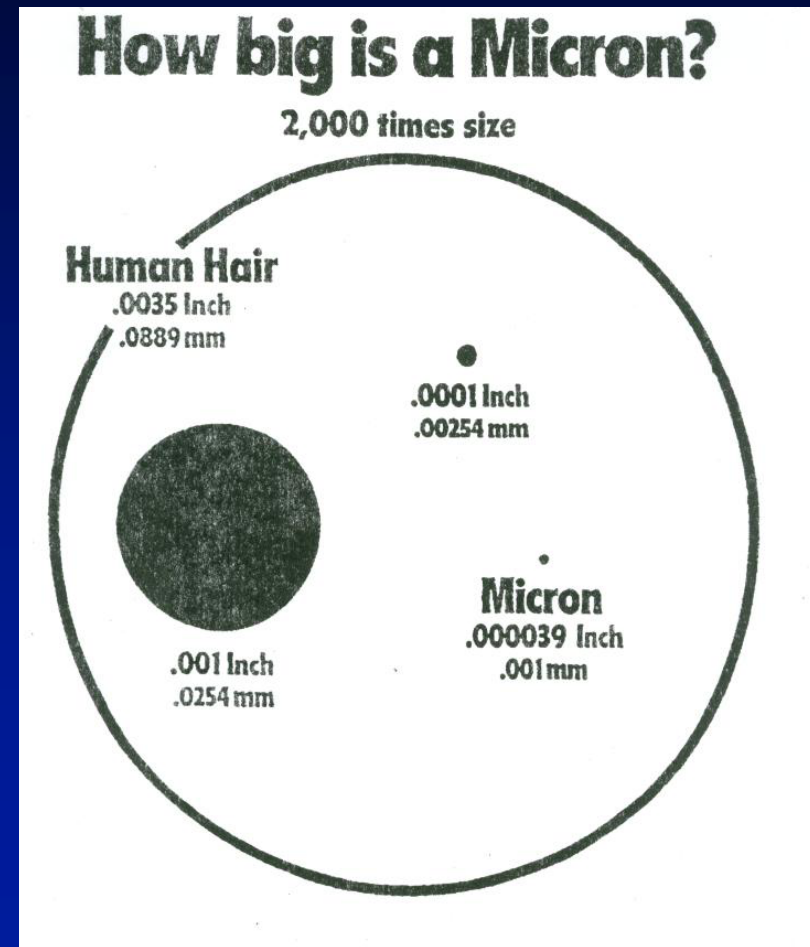
1 meter = 0.1 mR/hr

Radiolabeled Microspheres

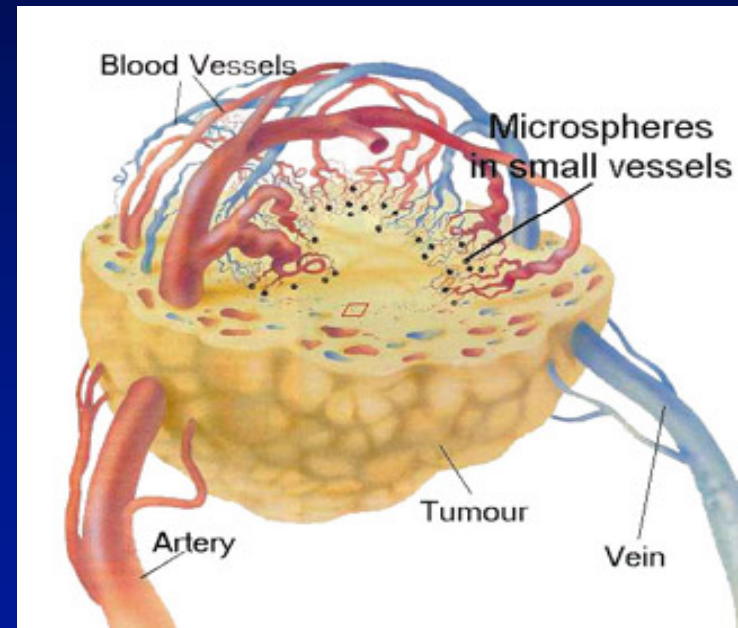
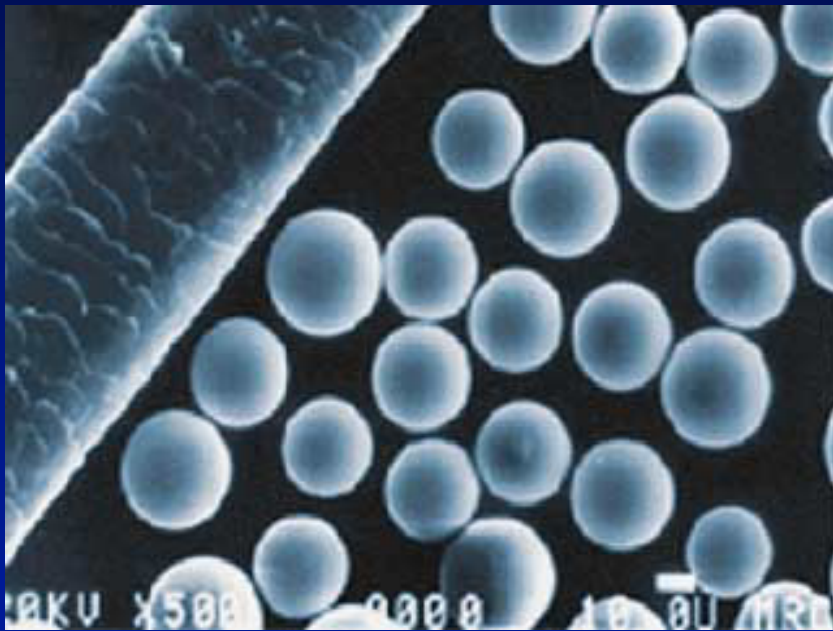
- ◆ **According to FDA, these are devices**
- ◆ **Labeled with Y-90**
- ◆ **Therasperes and SIR-Spheres differ by size and composition**
- ◆ **Only fully “approved” use is colorectal cancer metastatic to liver**
- ◆ **Serious adverse effects of improper deposition**
- ◆ **Expensive**

Physical Characteristics

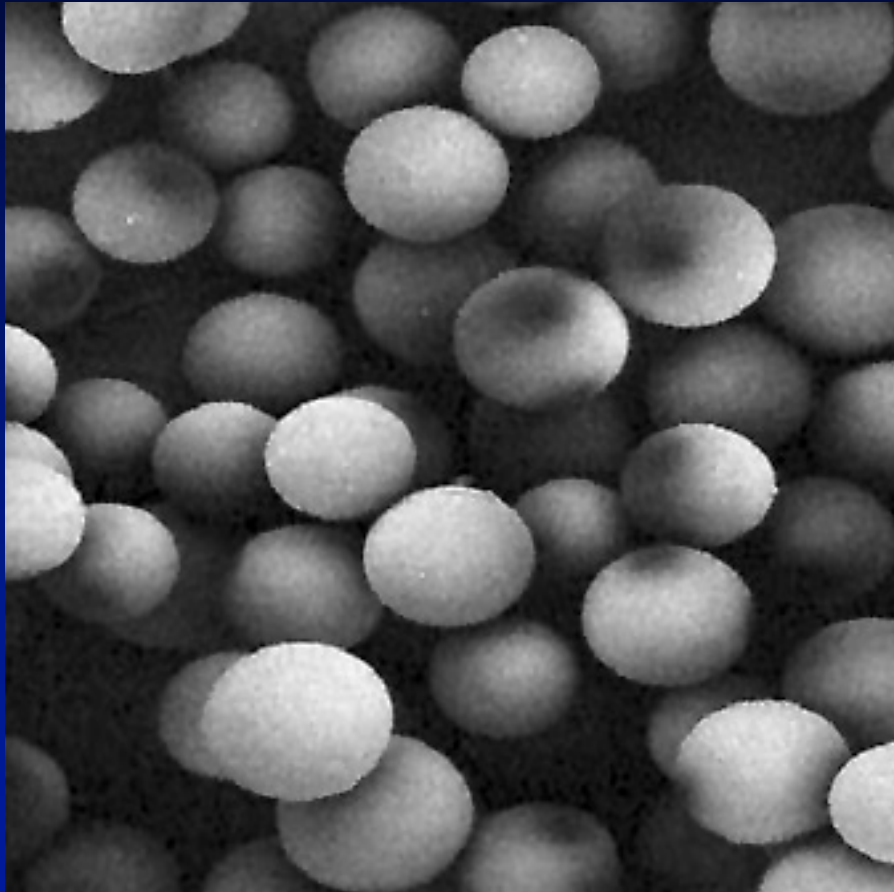
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Therapeutic Y-90 Spheres



Radiolabeled Microspheres



SIR-Spheres

Radiation Safety

- ◆ All **staff** should be using a radiation dosimeter, particularly **for the hands** where the most exposure is expected to occur.