SELECTIVE INTERNAL RADIATION THERAPY FOR TREATMENT OF LIVER CANCER

SIR-Spheres: A New Treatment Option for Non-Resectable Liver Tumors*

- Treatment Overview
  - SIRT: Selective Internal Radiation Therapy
    - Concept of SIRT
    - Science & Specifications of SIR-Spheres
- Published Outcomes
- Patient Selection
- Treatment Planning
  - Pre-Treatment Testing
  - Treatment Issues
    - MAA Spect
    - Dosimetry
    - Administration Technique
    - Side Effects
    - Discharge
    - Radiation Safety

SIRT Advantages

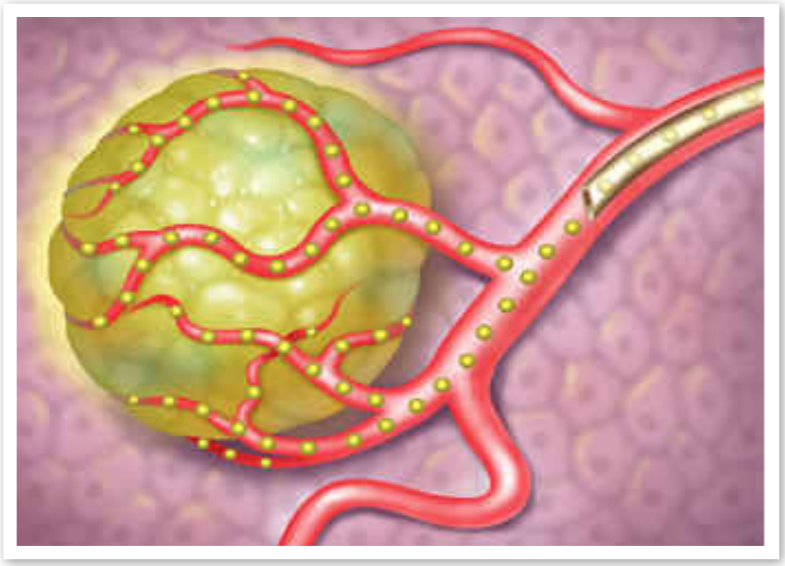
• Sphere treatment is a minimally invasive procedure and is usually performed as an outpatient procedure

• Spheres are reimbursed by Medicare when delivered as an outpatient procedure

• Spheres offer patients who have unresectable metastatic tumors an alternative therapy to prolong survival.

• SYS chemotherapy can resume 4 weeks after treatment

• Sphere treatment can downstage tumors and allow for surgical resection



Conclusions:

• All patients with liver cancer are potential candidates for SIRT

• SIRT needs a team for effective treatment

• SIR-Spheres are an adjunct to, not a replacement, for chemotherapy.

The earlier in the treatment process, the better the outcomes

•Sir-Spheres are active against all tumor sizes• Patient may be downstaged to resection following treatment

SIR-Spheres* Trademarked by SIRTEX SIR Spheres PTY Ltd sirtex.com

SIRT: SELECTIVE INTERNAL RADIATION THERAPY

Concept of SIRT

To selectively target a very high radiation dose to all tumors within the liver

while at the same time maintaining a low radiation dose to the normal liver tissue

- Y-90 Microspheres represent a new implantable radiotherapeutic device used to deliver Selective Internal Radiation Therapy or SIRT.

While we tend to think of Y-90 Microspheres as a radiopharmaceutical, it is actually an implantable "sealed source" and was approved by the FDA as a device rather than a radiopharmaceutical

- Two different manufacturers prepare Y-90 Microspheres. The similarities and differences between the two products are listed below:

SIMILARITIES

Y-90 SIR-Spheres (average size 30-35 microns)

Labeled with Y-90

94% of rad dose delivered within 11 days

Provide targeted radiation with an average tumor dose of 280-380 Gy, a much higher than can be achieved with external beam radiation.

The normal liver dose is less than 80 Gy

Maximum Beta Energy 0.93 MeV

Half life 64.1 hr

Avg penetration: 2.5 mm

Max penetration: 11 mm

Distributed non-uniformly

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DIFFERENCES

Y-90 SIR-Spheres

Polystyrene resin microspheres

Low radioactivity per sphere (50 Bq)

Specific gravity of saline; low density

40-60 Million spheres/dose
Higher probability of occlusion

Lower probability of administering prescribed dose

Manufactured in Australia

Y-90 Theraspheres

Glass microspheres

High radioactivity per sphere (4,000 Bq)

Specific gravity of glass > saline

0.5-2 Million spheres/dose

Lower probability of occlusion

Higher probability of administering prescribed dose

Manufactured in Canada

Concept of SIRT

• Approximately 20-40 million spheres are delivered using a microcatheter that is well advanced into the arterial system.

• The administration procedure is performed as an outpatient procedure. The patient can resume chemotherapy 4 weeks post treatment with SIRT.

• SIRT administration requires a coordinated multi-disciplinary team that includes:

Interventional Radiology

Radiation, Medical, Surgical Oncology

Nuclear Medicine, Radiochemist, Physicist, RSO

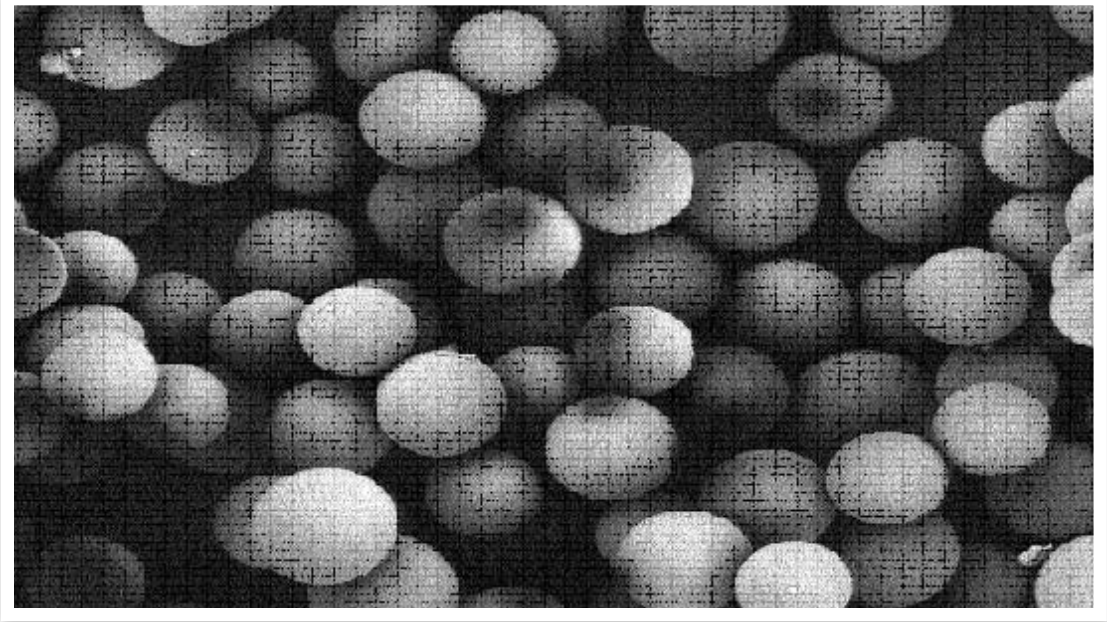
A designated program coordinator

• SIR-Spheres ® were approved by the FDA in March 2002 for Metastatic Colorectal Cancer Patients

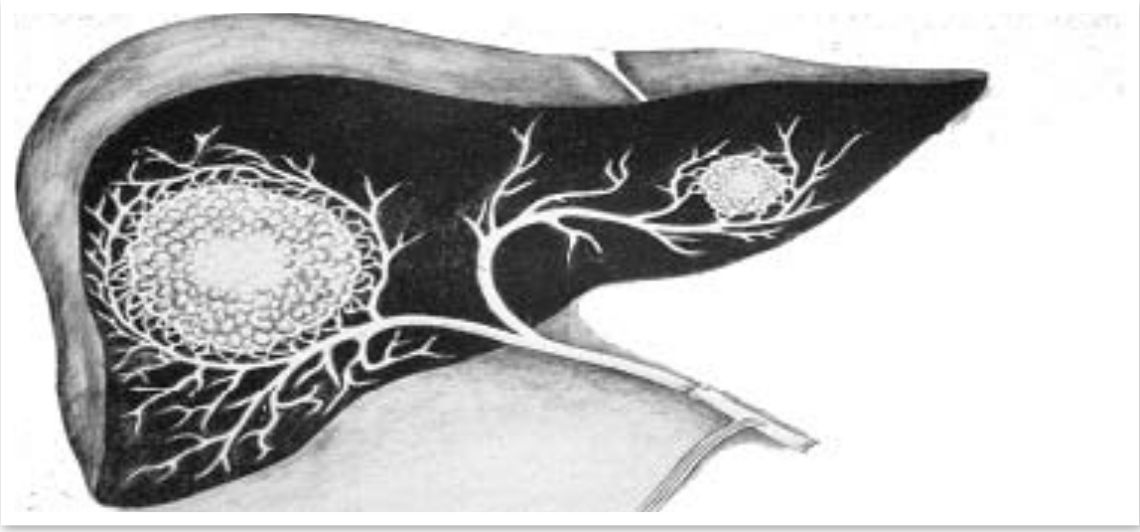
• Under the terms of the Medicare Prescription Drug Improvement and Modernization Act of 2003 Medicare reimburses the hospital at 100% cost to charge ratio for the outpatient treatment

• Currently there are hundreds of US treatment centers

• Tens of thousands of patients have been treated in the USA and worldwide.

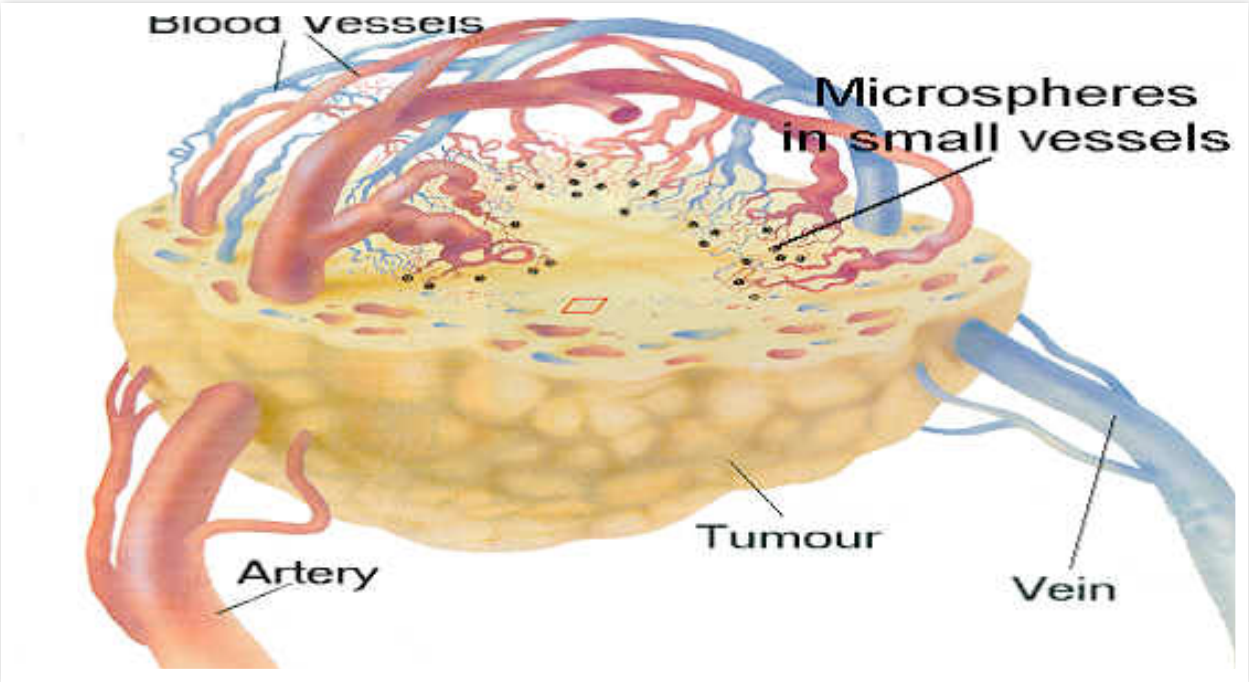


Blood Supply to the Liver



- Dual blood supply to the liver – hepatic artery + portal vein
- Tumors >2 cm draw >80% blood from the hepatic artery
- Normal liver parenchyma draws >80% blood from the portal vein

Hepatic artery supplies 90% of tumor; only 10% to normal liver



Specifications:

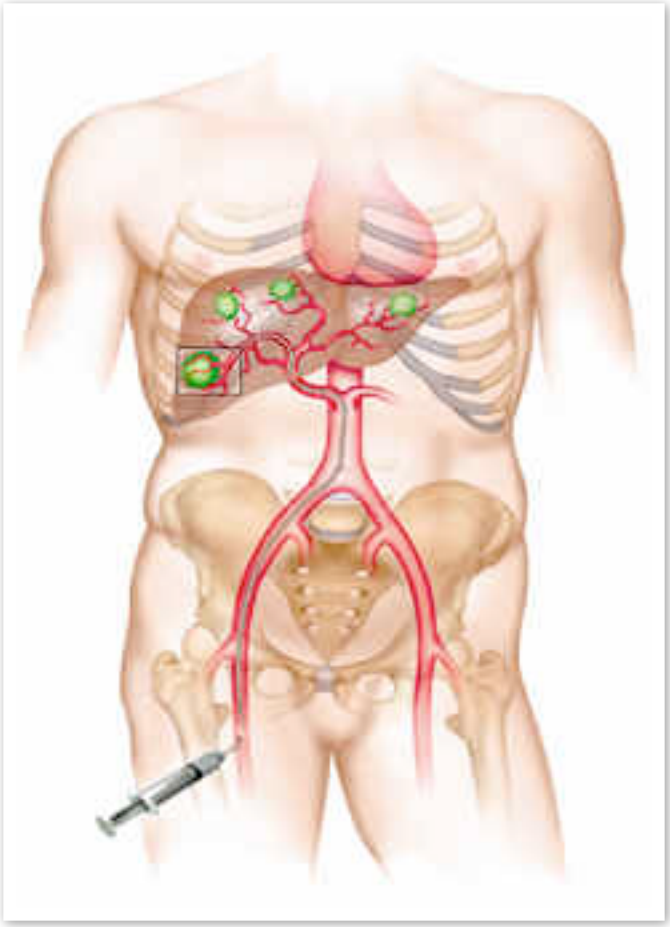
- Resin particles 20-40 microns in diameter (avg: 32 microns)
- Y90 = pure beta emitter chemically bound
- Max tissue penetration is 11 mm (avg 2.5 mm)
- Half life- 62.4 hours (~2.5 days)
- 94% of radiation dose is delivered within 11 days
- Low radioactivity per sphere (50Bq/sphere)
- Easily suspended in water-specific gravity of saline
- Slightly embolic
- Dose extracted from bulk individual dose

Entrapment of SIR-Spheres in Vascular Bed

SIR-Spheres Delivery Kit

Administration Technique: 2nd Outpatient Admission

SIR-Spheres Being Infused into the tumor



Phase III Randomized: SIRT + HAC FUDR

STUDY *	N = 70 patients	Time To Progression of Disease	SURVIVAL
HAC (FUDR) alone vs. SIRT + (FUDR)	34 HAC alone 36 SIRT + HAC	9.7 months 15.9 months P<0.001	1 yr - 2yr 68% 72% 39% 29%

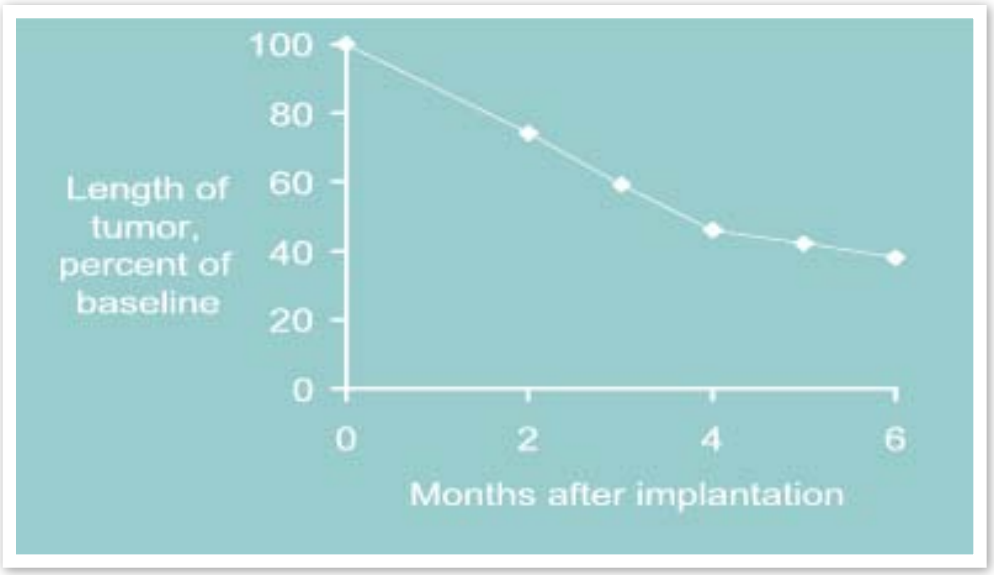
• FDA Study
•SIRT administered via an implantable port
•Previously untreated patients MCRC
*Gray B, Van Hazel, G ASCO proceedings 2003 , Journal of Surgical Oncology –2004:88:78-85

Phase III Randomized: SIRT + SYS 5FU + LV

STUDY *	N = 21 patients	TTP	SURVIVAL
SYS 5-FU/LV vs SIRT + 5-FU/LV	10 FU/LV alone 11 SIRT + FU/LV	3.6 months 18.6 months P=<0.005	12.8 months 29.4 months P=0.02

•SIRT administered via an angio catheter
•Previously untreated patients MCRC
*Gray B, Van Hazel, G Journal of Surgical Oncology 2004; :88:78-85

These data represent the median tumor length based on outcomes from 226 tumors in 64 clinical trial patients.



Selection:

- Liver dominant disease/Minor EHD
- Extensive angiogram work up/ some arterial embolization (GDA)
- Adequate hepatic function: Bilirubin should be no higher than 1.8-2.0
- Lung shunting less than 20% as determined by a MAA scan
- Patients should be taken off SYS chemotherapy 2-4 weeks prior to SIRT. SYS chemotherapy can resume 4 weeks after RX
- Not eligible for resection or transplant
- No other hepatic disease
- Adequate renal function
  creatinine < 150 µmol/L
- Adequate hematological function
  Granulocytes >1.5 x 109 /L
  Platelets >100 x 109 /L

Patient Work-Up

- CT scan showing unresectable liver malignancies within 28 days of SIRT
- Angiography
- CTHA
- MAA – lung shunting
- Patient workup procedure results in 5-10 % of patients not being eligible for SIRT

- Diagnostic Angiography prior to placement of SIR Spheres
  Technical issues: Groin /Arm / Type of Cath
  Anatomy: Replaced /Anomalous /Variants
  Selective / super-selective
  Portal vein patency
  Porto-venous shunts
  Coil embolization of GDA and RGA to prevent inadvertent spilling

PRE-TESTING- 1st Patient Outpatient Admission

- Chest x-ray
- Triple Phase CT Scan of abdomen, chest and pelvis
- Abdominal/pelvic ultrasound and bone scan?
- PET Scan/PET CT
- Baseline liver function testing to determine the extent of liver damage/dysfunction
- Diagnostic mesenteric angiography for vascular mapping

    Determines hepatic arterial anatomy

  - Assessment of variants in vascular anatomy

    Assesses risks of complications

  - Shunt through tumor vascular bed to lungs
  - Non-target embolization to adjacent organs

    Can convert a "non-candidate"

  - Prophylactic embolization of branches to GB, GI tract, pancreas

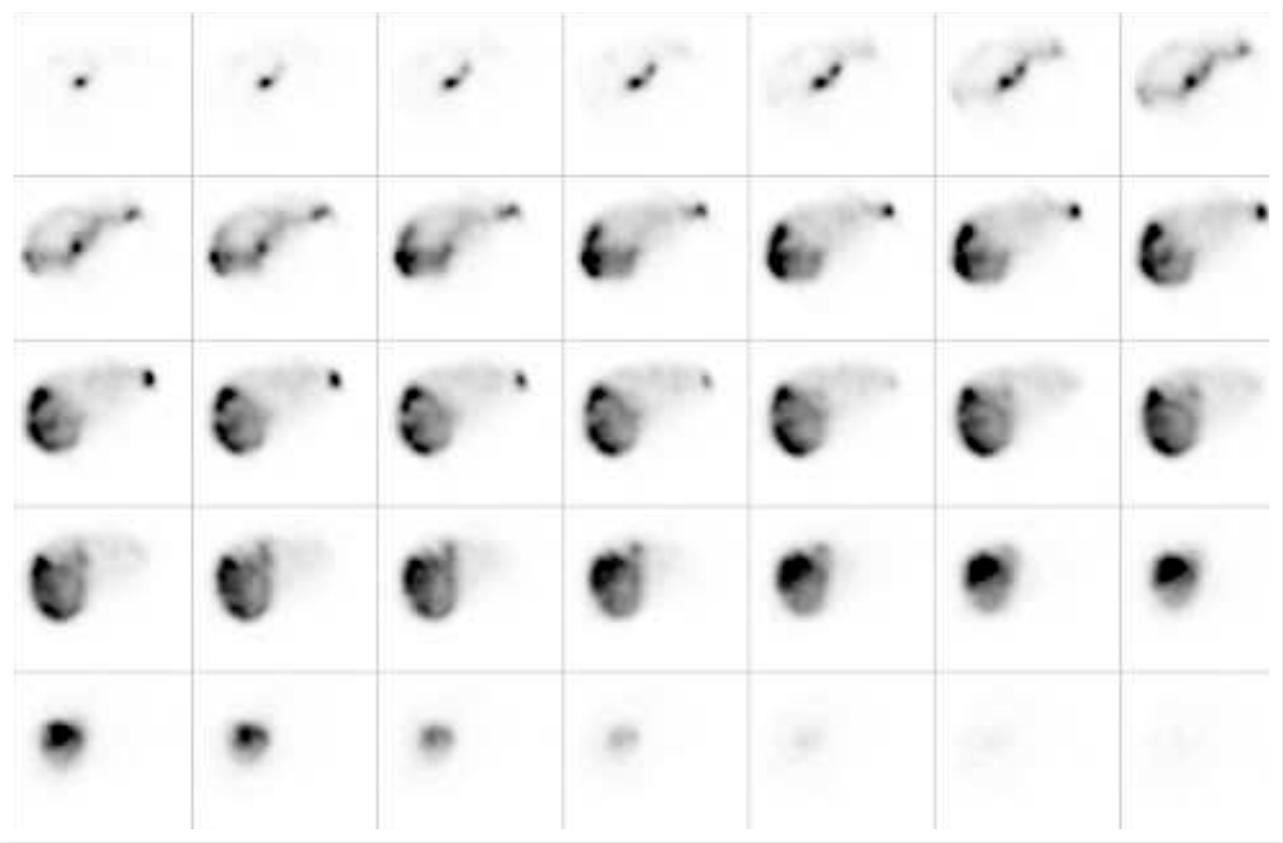
    Assessment of Anomalous Arteries

  - 50% of patients have aberrant arteries supplying the liver
  - 15% of patients have aberrant arteries from liver supplying the gut
  - Variant hepatic anatomy: Covey et al, Radiology, 2002; 224; 542-547

• MAA Spect

Tc-99m MAA STUDY: to determine pulmonary shunting that could result in non-targeted delivery to gastrointestinal tract

Maximum 20% shunting as this will deliver a total cumulative dose to the lung of 30 Gray - maximum tolerable dose of lungs



Lung Shunting- MAA

Admin Activity: GBq	Lung Shunting %	Lung Radiation Dose: Gray
1	10%	5
1.5	10%	7.5
2	10%	10
2.5	10%	12.5
3	10%	15
1	15%	7.5
1.5	15%	11.25
2	15%	15
2.5	15%	18.75
3	15%	22.5
1	20%	10
1.5	20%	15
2	20%	20
2.5	20%	25
3	20%	30

If >20%, do not treat

DOSIMETRY

Empiric Method- Based Upon Clinical Experience

Estimated Degree of Tumor Involvement in the Liver	Recommended Y^{90} Amount for Treatment
< 50%	3.0 GBq
25% to 50%	2.5 GBq
<25%	2 GBq

Note: Dose reduction required if lung shunt is greater than 10%

10-15% shunt (20% reduction)

15-20% shunt (40% reduction)

>20%= no RX

BSA Method

- Patient Weight
- % of Liver Tumor Involvement

Activity of SIR-Spheres in GBq	=	(BSA-0.2) + % of tumor involvement
		100
Example: BSA (2.0-0.02)	=	(1.8) + 30% of tumor involvement
		100

Whole liver dose= 2.1 GBq

Lobar= Right Lobe (60%) - 1.26 GBq

Left Lobe (40%) - 0.84 GBq

Treatment Planning

Treatment Algorithm:

- Initiate insurance certification process
- Consider pre-SIRT PET-CT (volumetric)
- Diagnostic mesenteric angiography
- MAA Shunting Study
- Joint treatment plan & calculation of dose (IR, Nuclear Med, Radiation Oncology)

    Lobar vs whole liver ?

SIRT Side Effects:

- Pain during the administration due to embolic effect of the spheres
- Nausea – anti-nausea medication is needed
- Lethargy – for 1-2 weeks after treatment, will subside with time and is a normal response to abdominal radiation
- Gastritis – due to reflux of spheres during administration

Exposure:

- Bremsstrahlung radiation is typically 15 mSv per Gbq at 15 cm from the patient's right side (initially)

Post – Treatment

- 23-hour hospital stay
- Single use room or low traffic area
- Non-pregnant nursing staff /visitors
- Nursing from left hand side of patient
- Minimize visitor number and time
- Shielding unnecessary

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Discharge Instructions

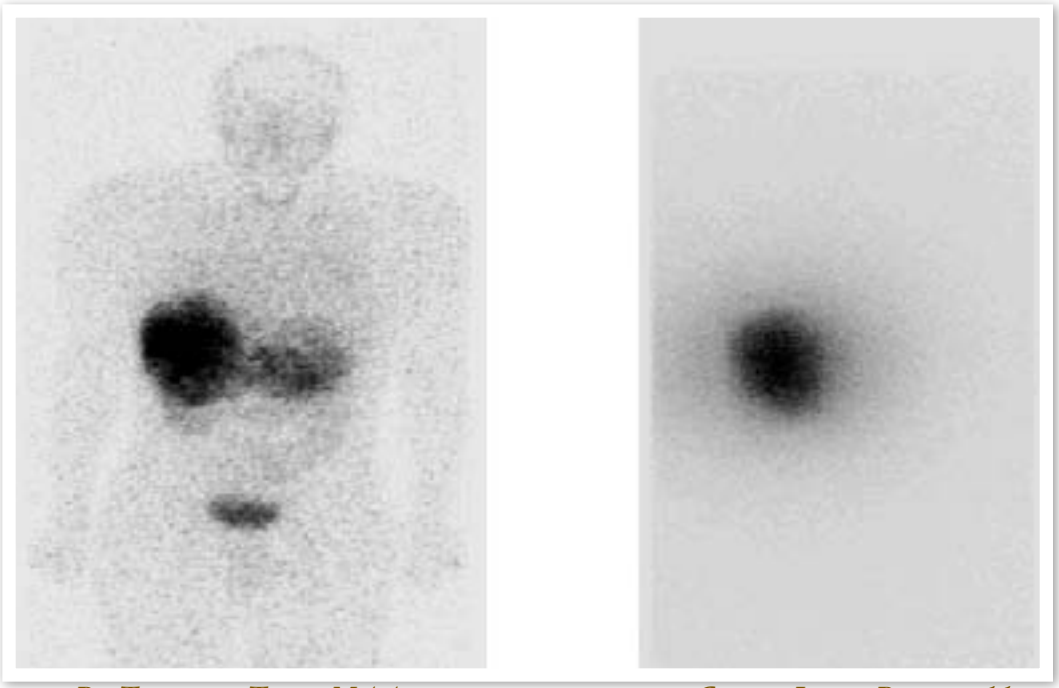
- Augmentin 500 mg or Cipro 500 mg for 5 days
- Anti-nausea suppositories
- Panadol Forte
- 8 glasses of water per day
- Make contact if nauseous/abdominal pain/fever greater than 102°F
- Resume light activity as soon as you feel like it

Clinical Studies

SIR-Spheres Treatment Outcomes:

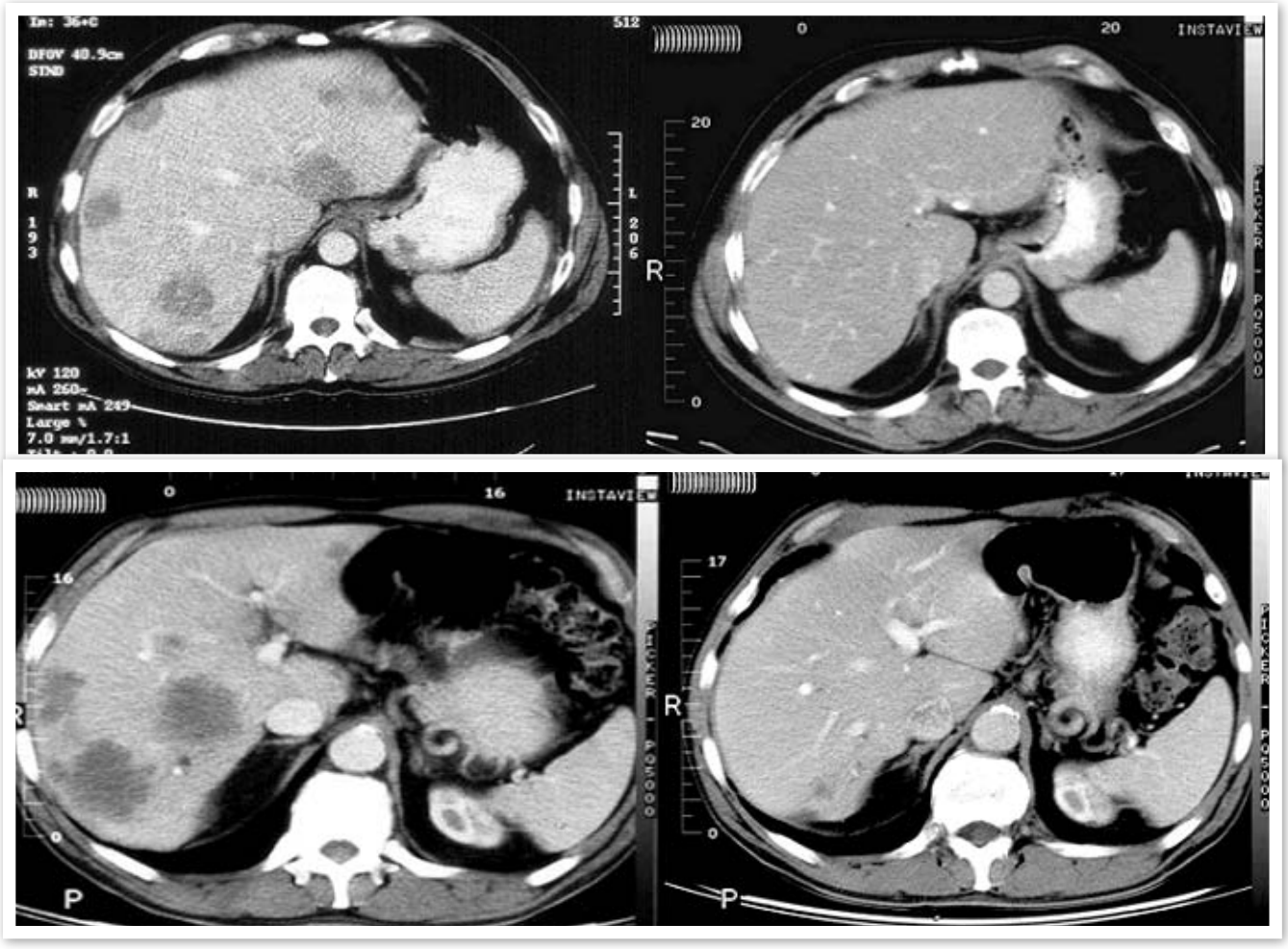
- > 20% of all tumors will clinically disappear
- Median time to elimination is 6 months
- Largest tumor to be eliminated had a baseline length of 100 mm
- Median reduction, irrespective of size, is - 60% (tumor 40% of baseline length)
- Largest linear reduction: 170 mm to 62 mm

Post Treatment Imaging

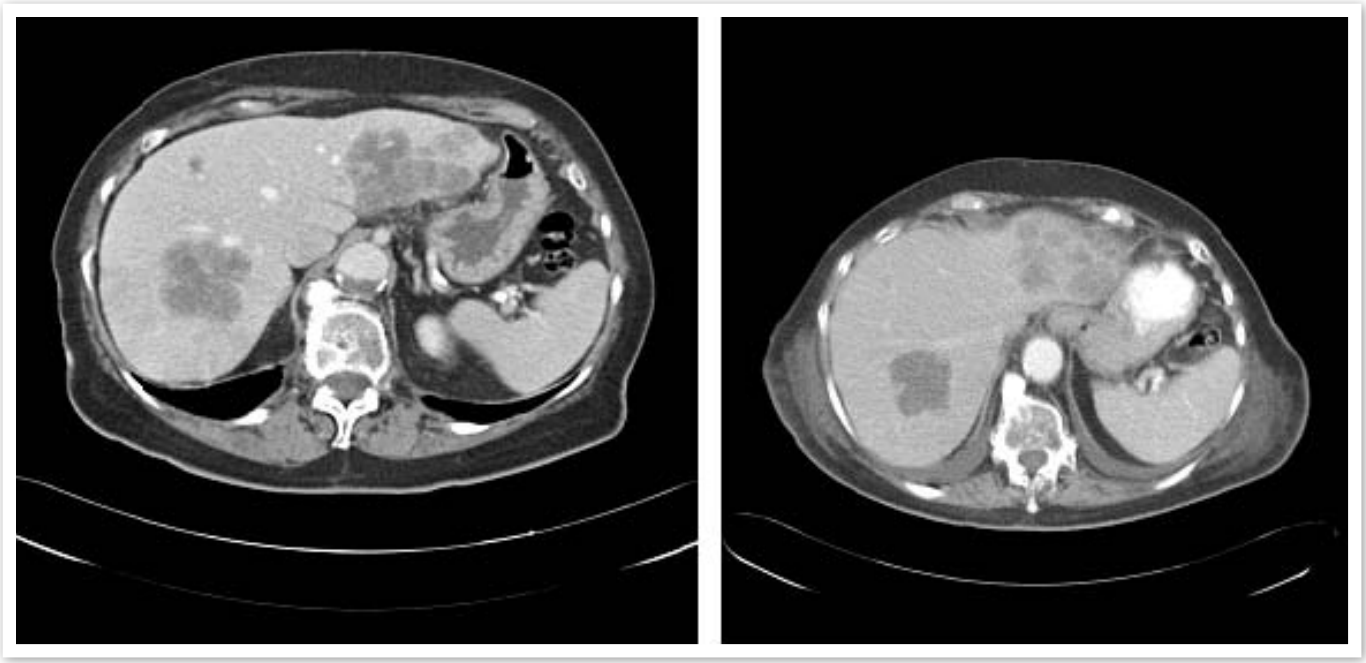


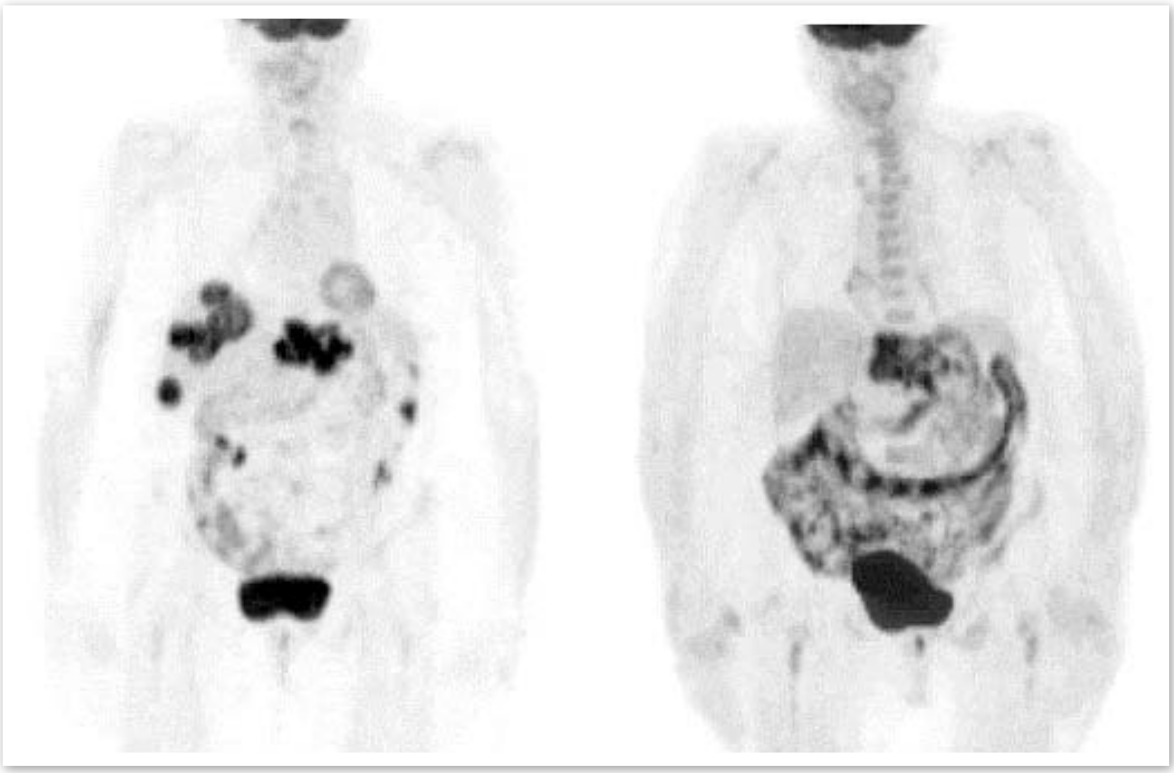
Pre Treatment- Tc99m MAA *Gamma Image- Bremsstrahlung*

Liver Metastases Derived From Colorectal Cancer – CT Scans



CR Mets- Treated: Right Lobe Only CT Scan Before and After SIRT





MCRC- Treated: Right Lobe Only: PET Scan Before and After SIRT