$^{90}$Y-Microspheres Radioembolization for Selective Internal Radiation Therapy of Primary and Metastatic Cancer in the Liver

« Aut tace aut loquere meliora silentio »
Concept of Selective Internal Radiation Therapy
(aka Radioembolization; Hepatic Artery Brachytherapy; Microbrachytherapy)

- To **selectively target** a very high radiation dose to all tumours within the liver, regardless of their cell of origin or location, while at the same time maintaining a low radiation dose to the normal liver tissue
- Infusion via hepatic artery, using differential blood supply to liver tumours thereby preferentially targeting tumours
- Uses $^{90}$Yttrium-labelleled microspheres
  - Half life: 64.1 hours
  - $\beta^-$ decay, $E_{\text{mean}} = 0.93$ MeV; $E_{\text{max}} = 2.28$ MeV
  - Penetrates tissue, mean 2.5 mm; max 11 mm
  - Achieves doses of 100–1,000+ Gy to tumour
Overview of Procedure

• Typically a 2-stage process
• Work-up procedure:
  – Trans-femoral catheter access to hepatic artery vasculature and identify tumour feeding vessels
  – Prophylactic occlusion of extra-hepatic vessels (GDA, right gastric etc)
  – Injection of $^{99m}$Tc-MAA / gamma camera study to assess lung-shunt
• Treatment procedure:
  – 1–3 weeks later
  – Reassessment of occlusion
  – Injection of microspheres dose
  – Optional gamma camera study to confirm implantation
  – Sequential lobar approach if necessary for patient safety
**Medical devices** (not radiopharmaceutical!)

*Resin microspheres* (SIR-Spheres®, SirTex)
- $^{90}$Y is within the spheres
- particle size: 20-60 µm; activity per particle: 50 Bq
- about 20-40 million particles per administration
- uniform dose biodistribution

*Glass microspheres* (TheraSphere®, MDS Nordion)
- $^{90}$Y is an integral constituent of the glass matrix
- particle size: 20-30 µm; activity per particle: 2500 Bq
- about 1-4 million particles per administration
- less embolic effect on microvessels and potential influence of gravity on biodistribution
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SIR-spheres®</th>
<th>TheraSphere®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>Resin</td>
<td>Glass</td>
</tr>
<tr>
<td>Particle size (μm)</td>
<td>20-60</td>
<td>20-30</td>
</tr>
<tr>
<td>Nb of spheres per vial (range in million)</td>
<td>40-80</td>
<td>1.2-8</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Embolic effect</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Activity per sphere (Bq)</td>
<td>40-70</td>
<td>2,500</td>
</tr>
<tr>
<td>Activity available (GBq)</td>
<td>3</td>
<td>3, 5, 7, 10, 15, 20</td>
</tr>
<tr>
<td>Handling for dispensing</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Splitting one vial for two or more patients</td>
<td>Possible</td>
<td>Not possible</td>
</tr>
<tr>
<td>Radiation precautions</td>
<td>Urine contamination (?)</td>
<td>None</td>
</tr>
</tbody>
</table>

From Salem, J Vasc Interv Radiol 2006 (modified)
Indications

- Predominant liver-dominant or liver-only disease
- No extra-hepatic manifestation
- Life expectancy >12 weeks
- ECOG performance status 0–2
- Failed 1st and 2nd line of chemotherapy
- Unresectable disease (evaluated by GI specialists)
- Preferable tumour types:
  - Liver metastases of colorectal cancer (CRC)
  - Hepatocellular carcinoma (HCC)
Exclusion Criteria for Radioembolisation
(relative contra-indications unless stated)

- Pregnancy [absolute]
- Ascites or other clinical signs of liver failure on physical exam [absolute]
- Abnormal organ or bone marrow function as determined by:
  - total bilirubin level $>2.0$ mg/dL ($>34$ μmol/L) in absence of reversible cause
  - serum albumin $<3.0$ g/dL
  - AST (SGOT)/ALT (SGPT) $>5 \times$ institutional ULN
  - creatinine $>2.5$ mg/dL
  - platelets $<60,000/\mu$L; leukocytes $<2,500/\mu$L; absolute neutrophil $<1,500/\mu$L
- Previous external radiation therapy to the liver
- Excessive tumour burden with limited hepatic reserve
- Abnormal blood circulation due to anatomic variations resulting in back-flow to the stomach, pancreas or bowel, compromised portal vein, unless selective/super-selective delivery is performed

Following work-up procedure:
- $>30$ Gy exposure to the lungs (pre-therapeutic scan) [absolute]
- Non-correctable shunting to the GI tract [absolute]

Specific Contraindications: SIR-spheres®

• **Contra-indications:**
  – Previous external beam radiation therapy to the major volume of the liver
  – Ascites or clinical liver failure
  – Abnormal vascular anatomy (significant reflux determined by angiogram)
  – Lung shunting of the hepatic artery blood flow greater than 20% (determined by intra-arterial 99mTc MAA scintigraphy)
  – Disseminated extra-hepatic malignant disease

• Under debate
  – Capecitabine (within previous or subsequent 2 months only ?)
  – Main portal vein thrombosis

• **Special warnings**
  – Excessive radiation to the normal liver parenchyma: radiation hepatitis
  – Inadvertent delivery to
    • gastrointestinal tract or pancreas: acute abdominal pain, acute pancreatitis or peptic ulceration
    • gall bladder: cholecystitis
  – High levels of radiation and/or excessive shunting to the lung: radiation pneumonitis

Antiangiogenetics (induce complications during angiography)
Specific Contraindications: Therasphere®

- **Contra-indications:**
  - Severe liver dysfunction or pulmonary insufficiency
  - Deposition to the gastrointestinal tract that may not be corrected by angiographic techniques
  - Shunting of blood to the lungs that could result in delivery of > 610.5 MBq of 90Y to the lungs

- **Special warnings (pre-treatment high risk factors):**
  - Infiltrative tumour type
  - “Bulk disease” (tumour volume > 70% of the target liver volume, or multiple tumour nodules)
  - AST or ALT > 5 times ULN
  - Bilirubin > 1 time ULN
  - Tumour volume > 50% combined with an albumin < 3 g/dl
  - Antiangiogenetics (induce complications during angiography)
Precautions

• Usual arteriography precautions
• Nursing personnel must be trained in radiation safety.
• Ensure minimum radiation exposure
• No drug interaction have been reported to date (however, discontinue the radiation sensitizers)
• Prophylactic administration of antiulcer medication (for 2 weeks) and steroids (for 5–7 days)
• Avoid pregnancy for at least 4 months following treatment
• Critical person for radiation protection = interventional radiologist
  => 40 treatments per year gives an extra dose of 1.9 mSv
Pretherapeutic Procedures

• Pre-therapy evaluation of serum liver enzymes, blood cell count, coagulation and creatinin

→ Patients with adequate hepatic reserve and good functional status will maximize the therapeutic effect with minimal risk to normal liver parenchyma

• Visceral angiography performed by high-speed multi slice CT:
  – to visualise hepatic vascular organisation and map tumour-perfusing vessels
  – to assess portal vein patency (verify the absence of portal venous thrombosis)
  – to place coils (embolize collateral vessels)

• CT for determination of tumor load

• FDG-PET for exclusion of extrahepatic manifestations and evaluation of hepatic disease (since the aim is palliative, a small extrahepatic tumour burden is not a contraindication)

  combined PET/CT preferable
Intra-arterial (via the hepatic artery) administration of 99mTc-Albumin Macro-Aggregates (+/- perchlorate to prevent unspecific extrahepatic free technetium):

- to assess arteriovenous liver/lung shunting
- to determine the optimal therapeutic dose-activity
  - Preferable < 10%
  - Dose reduction if shunt between 10% and 20%:
    - 10%-15% shunt volume: calculated dose minus 20%
    - 15%-20% shunt volume: calculated dose minus 40%
[99mTc]MAA Planar Scintigraphy

- Delineation of lung borders by the help of a flood phantom

\[\text{shunt} \sim 4\%\]
[99mTc]MAA SPECT-CT

- More sensitive than planar or SPECT images for detecting extrahepatic accumulations

Gallbladder => prevention of acute cholecystis

Stomach => pretreatment coiling of a gastric branch

First experience of hepatic radioembolization using microspheres labelled with yttrium-90 (TheraSphere): practical aspects concerning its implementation
Dosimetry

• BSA Model:
  – Recommended formula for most patients
    
    \[
    \text{Dose (GBq)} = \text{BSA (m}^2\text{)} - 0.2 + \frac{\text{volume tumour}}{\text{volume tumour + liver}}
    \]

  – Dose reduction used if increased lung shunt; some centres also adopt in low volume disease or for highly pre-treated patients

• Partition Model:
  – Only useful if the tumour can be localized in a discrete area and drawn as an Area of Interest on SPECT
    
    \[
    \text{Dose (Gy)} = \frac{\text{activity (GBq) x 49670}}{\text{mass (g)}}
    \]

• Empiric Model:
  – Dose adjustment according to the estimated tumour load in the liver:
    • < 25% liver replacement: 2 GBq
    • 25% to 50% liver replacement: 2.5 GBq
    • > 50% liver replacement: 3 GBq

  Not recommended (increased risk of radiation-induced side effects)
Administration

Before treatment:

Coiling of the gastroduodenal artery (and optionally the right gastric artery/pancreaticoduodenal branches) to avoid deposition in the duodenum, stomach or pancreas

Treatment:

Administration of microspheres via a percutaneous transfemoral hepatic artery catheter to each hepatic lobe separately via the right and left hepatic artery

Pulsatil gentle infusion (no pressure) to strictly avoid back-flow using a specially designed manufacturer’s device.
<table>
<thead>
<tr>
<th>AE</th>
<th>Incidence</th>
<th>Characteristics</th>
<th>Prevention/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt;50%</td>
<td>mild (grade 1*) onset on Tx day for up to 1 week</td>
<td>none normally required</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>~50%</td>
<td>acute onset during Tx self-limiting; normally &lt;24 h</td>
<td>may require narcotic &gt; oral analgesia</td>
</tr>
<tr>
<td></td>
<td>~10% grade 3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>~40%</td>
<td>highest in Tx-experienced; normally &lt;24 h</td>
<td>prophylactic anti-emetics</td>
</tr>
<tr>
<td></td>
<td>&lt;5% grade 3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>~40%</td>
<td>onset in 1st month post-SIRT, normally subsides within 2 weeks</td>
<td>adequate nutrition &amp; hydration; prophylactic oral steroids</td>
</tr>
<tr>
<td></td>
<td>&lt;5% grade 3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>~20–40%</td>
<td>particularly in combination with chemo or HCC/cirrhosis; transient; resolves in days (ALT, AST), weeks (bilirubin) or months (alb.)</td>
<td>none normally required</td>
</tr>
<tr>
<td></td>
<td>1–6% grade 3–4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CTC 2.0
## Potential Complications

<table>
<thead>
<tr>
<th>SAE</th>
<th>Incidence</th>
<th>Characteristics</th>
<th>Prevention/action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation gastritis or duodenitis</td>
<td>~5–10%</td>
<td>non-target administration; immediate, severe unremitting pain</td>
<td>meticulous technique &amp; occlusion of GI arteries; prophylactic PPI for 1 mo</td>
</tr>
<tr>
<td>Radiation pancreatitis</td>
<td>&lt;1%</td>
<td>non-target administration; immediate, severe unremitting pain</td>
<td>meticulous technique &amp; occlusion of GI arteries</td>
</tr>
<tr>
<td>Radiation cholecystitis</td>
<td>&lt;1%</td>
<td>non-target administration; right upper quadrant pain</td>
<td>various technical approaches; may require cholecystectomy</td>
</tr>
<tr>
<td>Radiation-Induced Liver Disease (RILD)</td>
<td>&lt;1%</td>
<td>excess radiation to normal liver; onset typically 30–90 d post-SIRT; permanently elevated LFTs, portal hypertension, eventual fibrosis</td>
<td>appropriate dosimetry (BSA); dose reduction in patients with reduced hepatic reserve</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>no cases since lung-shunt study</td>
<td>excessive radiation delivery to lung tissue</td>
<td>routine lung-shunt study; maintain &lt;30 Gy to lung</td>
</tr>
</tbody>
</table>
Side Effects

• Common side effects:
  – Fatigue
  – Abdominal pain
  – Nausea
  – Fever
  – Transitory elevation of transaminases

• Possible severe adverse events (2-8%):
  – Chronic abdominal pain
  – Nontarget irradiation and/or attenuated irradiation in adjacent structures:
    • radiation-induced gastric disease (gastritis, gastrointestinal ulceration, upper gastrointestinal bleeding, pancreatitis)
    • radiation-induced lung disease (pneumonitis, right pleural effusion)
    • radiation-induced liver disease (hepatitis, hepatic fibrosis and portal hypertension, cholecystitis)
Biodistribution evaluation

\[ ^{90}Y \]

Half-life: 64.1 h
\[ \beta^- \text{ decay, } E_{\text{max}} = 2.28 \text{ MeV} \]
Internal pair-production, 0.000032 per decay
Bremsstrahlung spectra from Y-90 in water phantom

- HE collimator
- LEAP collimator
- Without collimator

Intensity vs. Energy [keV]
PET/CT images

- 90Y PET/CT (one or two frames of 30 minute)
  - Confirmation of microspheres distribution
  - Estimation of treatment efficacy?
Follow-up

• At 30 days and at 2- to 3-month in order to assess:
  – treatment-emergent side effects
  – tumour response

• Parameters to assess the result of treatment:
  – determination of tumour load, volume and serum tumour markers (AFP, CEA)
BEFORE SIRT

AFTER SIRT
good response
BEFORE SIRT

AFTER SIRT

minor response
Consultation – Tumour Board
Medical Oncology   Radiation Oncology
Surgical Oncology   Nuclear Medicine
Interventional Radiology
Consensus for liver-directed therapy with \( {^{90}}Y \)-microspheres

1–2 weeks

Pre-Treatment Screening Evaluations

Tumour mapping

Abdominal CT and/or MRI

Liver-predominant disease

1–2 weeks

Team reviews imaging, proposed dose, planned tumour volume, and optimal catheter placement for radioembolization

1 week

Delivery of \( {^{90}}Y \)-microspheres to the planned treatment volume

same day

Bremsstrahlung (gamma) scan
Post-implant QA documentation

1 week

Vessel mapping

Hepatic angiogram, protective embolization of extra-hepatic vessels and \( {^{99m}}Tc \)-MAA scan

Safe delivery achievable

Where do microspheres fit as a liver treatment?

- EU approval for treatment of unresectable liver tumours
- Loco-regional therapy: no impact on extra-hepatic disease
- Used in liver-only or liver-dominant disease:
  - in combination with systemic chemotherapy for...
    - mCRC (at 1st-line, 2nd-line etc)
    - in trials with systemic chemo for mNET and pancreatic cancer (at 1st-line, 2nd-line)
  - as monotherapy for...
    - mCRC and other metastatic disease (salvage in chemo-refractory)
    - HCC (at 1st-line, 2nd-line)
    - mNET (at 1st-line, 2nd-line etc)
    - Cholangiocarcinoma (at 2nd-line etc)
- Studies suggest earlier use provides greater benefits
- Potential for down-staging to resection or ablation
SIR-Spheres microspheres + FOLFOX4 in mCRC: CT Response

Patient 2: Baseline CT scan pre-SIRT

Patient 2: CT scan 6 months post-SIRT

SIR-Spheres microspheres + FOLFOX4 in mCRC: CT Response

Patient 3: Baseline CT scan pre-SIRT

Patient 3: CT scan 6 months post-SIRT; patient was subsequently resected

SIR-Spheres + irinotecan in >2\textsuperscript{nd}-line mCRC: CT Response

Baseline CT scan pre-SIRT

Scan 3 months after implantation

Conclusion

• $^{90}$Y-microspheres with delivery into the hepatic artery is a promising new local therapy

• Data on comparing this treatment alone or in combination with other modalities, particularly systemic or local chemotherapy must be awaited

• However, response rates are sufficiently high to make it likely that this treatment will have useful impact on the management and survival of patients

• The treatment seems to be less appropriate as a stand alone modality but should rather be considered in conjunction with modern chemotherapy or other local treatment modalities
Issues requiring further clarification

• Benefits of the treatments (survival gain, progression free survival and quality of life) assessed by prospective studies
• Minimum / optimal time interval between repeated treatments
• Comparison between radioactive ligands
• Therapeutic potential of 188Re-Lipiodol
• Role of combined therapy