Y-90 SIR-Spheres Treatment of Unresectable Primary or Metastatic Liver Tumors

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Localised Liver Cancer

- Surgery
- Laser & Sclerotherapy
- RF Ablation
- Cryotherapy
Advanced Liver Cancer
Hepatic Vasculature
Blood Supply of Liver Cancer
Blood Supply to Liver Cancer
Concept of SIRT
S(selective) I(internal) R(radiation) T(therapy)

To selectively target a very high radiation dose to all tumors within the liver, regardless of their cell of origin, number, size or location

*while at the same time*

Maintaining a low radiation dose to the normal liver tissue
- 32μ diameter
- Yttrium⁹⁰
- Beta 0.93MeV
- 64.1hrs half life
- Penetration
  - 2.5mm mean
  - 11mm max
SIR-Spheres in Liver Cancer
Entrapment of SIR-Spheres in Vascular Bed
Dosimetry

1. ARTERIAL BLOOD FLOW
2. SPHERE DENSITY
3. SPHERE SPECIFIC ACTIVITY
4. SPHERE NUMBER

HYPERVASCULAR RIM

HYPOVASCULAR CORE
Types of SIRT

- **Y-90 Theraspheres**
  - Nordion
  - Glass beads (heavier)
  - High specific activity
  - Fewer number of beads
  - Approved for HCC only (with IRB approval)

- **Y-90 SIR Spheres**
  - SIRTEX
  - Plastic
  - Lower specific activity
  - Large number of beads
  - Approved for Colorectal Carcinoma
  - Used off-label for many other liver tumors
SIR-Spheres
Administration technique
Y-90 microsphere selective radiation therapy

- A microcatheter is selectively placed in the hepatic artery or its branches through the femoral artery and celiac trunk by IR.
- Microspheres lodged in the microvasculature in the tumor, deliver localized radiation.
Transfemoral Injection
OBJECTIVES

To evaluate the efficacy and safety of Y-90 SIR-Spheres (SirTex) treatment in pts with unresectable liver tumors.
METHODS

- 109 Pts. (130 treatments)

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>46</td>
<td>42.2</td>
</tr>
<tr>
<td>NETs</td>
<td>10</td>
<td>9.2</td>
</tr>
<tr>
<td>HCC</td>
<td>32</td>
<td>29.4</td>
</tr>
<tr>
<td>Colon ca</td>
<td>10</td>
<td>9.2</td>
</tr>
<tr>
<td>Other ca</td>
<td>11</td>
<td>10.1</td>
</tr>
</tbody>
</table>
### Patient Population

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>%</th>
<th>Median Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>69</td>
<td>63.3</td>
<td>60 (38-85)</td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>36.7</td>
<td>67 (45-75)</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>100</td>
<td>63 (38-85)</td>
</tr>
</tbody>
</table>
Tumours in both lobes of Liver
Super Selective Injection of SIR-Spheres
$^{99m}$Tc-MAA Scan

- To assess liver arterial perfusion, lung & intra-abdominal shunting
- Dose: 5 mCi $^{99m}$Tc-MAA
- Inject into the hepatic artery via a percutaneous catheter
- Anterior and posterior planar images from the head to the thighs
- SPECT/CT images of the abdomen
MAA Hepatic perfusion Imaging is routinely performed prior to Y-90 therapy

Whole Body Planar A/P

SPECT/CT images of abdomen
Assess Lung Shunting

- ROIs were drawn around the liver and each lung in the anterior & posterior views
Assess Lung Shunting

- Geometric mean counts for the liver & the lungs were then obtained.

\[
\text{% Shunt} = \frac{\text{Lung Counts} \times 100\%}{(\text{Liver} + \text{Lung}) \text{ Counts}}
\]
Diagnostic Studies: Arterial Tc-99m MAA
Diagnostic Studies: Arterial Tc-99m MAA
SIRT Dose Calculation

SIR-Spheres Dose (GBq)

\[
\text{SIR-Spheres Dose (GBq)} = BSA (m^2) - 0.2 + \frac{\text{volume tumour}}{\text{volume tumour} + \text{liver}}
\]

% Lung Shunting % Dose
Reduction

0-10 % 0 %
10-15 % 20 %
15-20 % 40 %

40% Coldwell Reduction (before 7/2006)
25% Coldwell Reduction (after 7/2006)
Volume reduction
Post-Therapy Y-90 Bremssstrahlung Scan
Post-Therapy Y-90 Bremmsstrahlung Scan
Example of good MAA / Y-90 match
Follow Up

• Radiological (CT, MR, PET/CT or Octreoscan)
• Tumor markers
• F/U of at least 3 months was available
• Toxicity - symptoms
### Follow Up Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Pts. (Tx)</th>
<th>Carcinoid + NET</th>
<th>HCC + Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>109 (130)</td>
<td>58 (74)</td>
<td>51 (56)</td>
</tr>
<tr>
<td>NA</td>
<td>38 (48)</td>
<td>16 (24)</td>
<td>22 (24)</td>
</tr>
<tr>
<td>Follow up</td>
<td>71 (82)</td>
<td>42 (50)</td>
<td>29 (32)</td>
</tr>
</tbody>
</table>
### Prescribed Dose*

<table>
<thead>
<tr>
<th>Dose</th>
<th>No.</th>
<th>%</th>
<th>Median (GBq)</th>
<th>Min. (GBq)</th>
<th>Max. (GBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. Dose.</td>
<td>18</td>
<td>21.95%</td>
<td>1.55</td>
<td>1.20</td>
<td>2.48</td>
</tr>
<tr>
<td>Dose Reduction (25-40%)</td>
<td>64</td>
<td>78.05%</td>
<td>1.20</td>
<td>0.30</td>
<td>2.05</td>
</tr>
</tbody>
</table>

*Std. Dose (GBq) = BSA(m²) - 0.2 + \( \frac{Tumor \ Vol}{(Tumor + perfused \ liv) \ Vol} \)*
### SIR-Spheres Infusion

<table>
<thead>
<tr>
<th>Targeted Lobes</th>
<th>Tx No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Liver</td>
<td>20 (24.4%)</td>
</tr>
<tr>
<td>Right Lobe</td>
<td>47 (57.3%)</td>
</tr>
<tr>
<td>Left Lobe</td>
<td>15 (18.3%)</td>
</tr>
</tbody>
</table>
## RESULTS

### Lung Shunting

<table>
<thead>
<tr>
<th>Lung Shunting (%)</th>
<th>Median</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6</td>
<td>1.1</td>
<td>18.0</td>
</tr>
</tbody>
</table>
**RESULTS: Hepatic Tumor Volume%**

<table>
<thead>
<tr>
<th>% of Volume</th>
<th>No. (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25%</td>
<td>24 (29.3%)</td>
<td>8.7-24.0</td>
</tr>
<tr>
<td>25-50%</td>
<td>50 (61%)</td>
<td>25-48.5</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>8 (9.7%)</td>
<td>51.0-72.0</td>
</tr>
</tbody>
</table>
## RESULTS: SIRT Dosimetry

<table>
<thead>
<tr>
<th>Absorbed Dose (Gy)</th>
<th>Median</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>9.88</td>
<td>1.8</td>
<td>30</td>
</tr>
<tr>
<td>Liver</td>
<td>21.9</td>
<td>5.2</td>
<td>70</td>
</tr>
<tr>
<td>Tumor</td>
<td>60.3</td>
<td>6.4</td>
<td>204</td>
</tr>
<tr>
<td>T/N</td>
<td>2.9</td>
<td>0.76</td>
<td>11.4</td>
</tr>
</tbody>
</table>
## RESULTS: Objective Response

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Response</td>
<td>41 (50%)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>2 (2.44%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>39 (47.5%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>22 (26.8%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>19 (23.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
</tr>
</tbody>
</table>
12 month post therapy CT showing interval regression in tumor volume.
Follow-up CT showing interval progression of disease
Treatment Response

- CR+PR: 54.8%
- SD: 52.6%
- PD: 33.3%

- Carcinoid+NET: 30.6%
- HCC: 11.1%
- Others: 15.5%

- Carcinoid+NET: 44%
- HCC: 38.9%
### RESULTS: Delivered Dose

<table>
<thead>
<tr>
<th>% of Rx Dose</th>
<th>Tx No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~100</td>
<td>63 (76.8%)</td>
</tr>
<tr>
<td>47-91% (Flow stasis)</td>
<td>19 (23.2%)</td>
</tr>
</tbody>
</table>

- There was no statistically significant difference in response between the groups treated with complete dose vs. partial dose due to flow stasis.
Side Effects

- Occasional symptoms
  - Nausea
  - Anorexia
- No radiation pneumonitis and treatment-induced liver failure
- 3 pts developed gastric ulceration (3%)
  - 2 pts were managed conservatively
  - 1 pt had surgical treatment
The Images of Gastric Biopsy

Ulceration and radiation fibroblasts

Microspheres in Stomach
Potential complications of Y-90 therapy caused by extra-hepatic distribution

- Radiation pneumonitis from hepatopulmonary shunting.

- Gastrointestinal ulcers and pancreatitis from gastrointestinal or pancreatic deposition of Y-90 microspheres.
CONCLUSIONS

• Y-90 SIR-Spheres treatment is a useful modality with remarkable objective response rate in the treatment of pts with unresectable primary or metastatic liver tumors.

• Pts with carcinoid or NET and other cancers showed a higher PR rate compared to pts with HCC.

• Partially delivered dose due to flow stasis could still produce a response.

• The procedure had acceptable toxicity.
Characterization of extra-hepatic distribution on MAA hepatic perfusion imaging for Yttrium-90 therapy


Mount Sinai Medical Center, NY
Objectives of the study

- We retrospectively reviewed all the MAA hepatic perfusion studies between 2007 to 2008 in Mount Sinai hospital.

- To characterize the extra-hepatic MAA distribution and correlate with *diagnosis, infusion site, and angiograms*.

- To characterize the *main cause* of the abnormal findings on MAA hepatic perfusion imaging.
## Patient population

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>83</td>
<td>(42%)</td>
</tr>
<tr>
<td>HCC</td>
<td>66</td>
<td>(33%)</td>
</tr>
<tr>
<td>Colon Ca</td>
<td>25</td>
<td>(13%)</td>
</tr>
<tr>
<td>Cholangio Ca</td>
<td>7</td>
<td>(4%)</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>(8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>198</strong></td>
<td></td>
</tr>
</tbody>
</table>
MAA injection site

Studies

RHA  101
LHA  43
PHA/CHA  54
### RESULTS I: Hepatopulmonary Shunting

<table>
<thead>
<tr>
<th>Severity</th>
<th>No.</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>17</td>
<td>20-40% dose reduction</td>
</tr>
<tr>
<td>Severe</td>
<td>6</td>
<td>Rejected for therapy</td>
</tr>
</tbody>
</table>
Moderate and severe lung shunting is overrepresented by the HCC group.

**Moderate lung shunting (10-20%)**
- HCC: 10/17 (59%)
- Carcinoid: 5/17 (29%)
- Colon Cancer: 2/17 (12%)

**Severe lung shunting (>20%)**
- HCC: 5/6 (83%)
- Carcinoid: 1/6 (17%)

**Total studies**
- HCC: 66/198 (33%)
- Carcinoid: 83/198 (42%)
- Colon Cancer: 2/198 (1%)
- Cholangiocarcinoma: 1/198 (0.5%)
Hepatic arterial-portal shunting

Severe lung shunting (89%)

Significant hepatic arterial to portal shunting

Esophageal varices
Mechanism of gastrointestinal and pancreatic deposition

1. Reflux (retrograde flow)
2. Anterograde flow through GDA, R/L gastric artery.
## RESULTS II: Abdominal extra-hepatic MAA deposition

<table>
<thead>
<tr>
<th>Cause identified &amp; corrected</th>
<th>Rejected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>GI/pancreas</td>
</tr>
<tr>
<td>Spleen</td>
<td>2</td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>5</td>
</tr>
</tbody>
</table>
Abdominal distribution is injection site dependent

<table>
<thead>
<tr>
<th></th>
<th>LHA</th>
<th>P/C HA</th>
<th>RHA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical vein</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>GI, Pancreas</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>
Distribution in the stomach and pancreas due to gastroduodenal artery (GDA)
Distribution in the stomach due to aberrant anatomy - a replaced right gastric A from PHA
MAA Deposition in the spleen and small intestine due to hepatic artery stenosis and extensive collateral flow
Conclusion I

For hepatopulmonary shunting:

1. Hepatopulmonary shunting appears to be associated with HCC more than other tumors.

2. Patients with severe lung shunting predominantly have a diagnosis of HCC.
Aberrant Arteries

- 50% of patients have aberrant arteries supplying the liver
- 15% of patients have aberrant arteries from liver and supplying the gut
Conclusion II

For abdominal extra-hepatic MAA deposition

1. MAA deposition in the stomach, intestine, pancreas and umblical vein predominantly occurs when injection is made into the LHA or P/CHA.

2. GDA and small gastric arteries are the main causes of distribution in the GI and pancreas, which are potentially correctable.
Conclusion III

- MAA hepatic perfusion imaging is useful in detection of extra-hepatic deposition.
Acknowledgement

Carcinoid Cancer Foundation™
Results of treating Colorectal Metastases with SIRT
Phase 2 Trial of SIR-Spheres

SIR-Spheres Alone 16 Patients

Response

- CT  73% decrease in tumor size (mean 48%)
- CEA  100% decrease in CEA (mean 78%)

Phase 2 Trial of SIR-Spheres

SIR-Spheres plus HAC 71 Patients

Response

- CT- 86% decreased tumor size (75% PR + CR)
- CEA – 95% decreased (89% PR + CR)

1st Randomised trial in advanced colorectal liver metastases (74 patients)  
HAC versus HAC + SIRT

<table>
<thead>
<tr>
<th>Response (CR + PR)</th>
<th>HAC</th>
<th>HAC + SIRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CT Response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>6 (18%)</td>
<td>16 (44%)</td>
</tr>
</tbody>
</table>

*Difference between groups p=0.02*

1st Randomised trial in colorectal liver metastases

**HAC versus HAC + SIRT**

<table>
<thead>
<tr>
<th>(CT Response)</th>
<th>HAC</th>
<th>HAC + SIRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>10.1 months</td>
<td>19.2 months</td>
</tr>
<tr>
<td>Median</td>
<td>9.8 months</td>
<td>16.0 months</td>
</tr>
</tbody>
</table>

*Difference between groups (Logrank test) p=0.001*

---

## 1st Randomised trial in colorectal liver metastases

**HAC versus HAC + SIRT**

### Survival

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAC</td>
<td>68%</td>
<td>29%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>HAC + SIRT</td>
<td>72%</td>
<td>39%</td>
<td>17%</td>
<td>4%</td>
</tr>
</tbody>
</table>

2nd Randomised trial in colorectal liver metastases
Systemic FU/LV versus SIRT + FU/LV

Time to Disease Progression Data:

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>4.7 months</td>
</tr>
<tr>
<td>SIRT + Chemotherapy</td>
<td>15.6 months</td>
</tr>
</tbody>
</table>

Comparison between groups $p < 0.0005$
ASCO 2002:599
2\textsuperscript{nd} Randomised trial in colorectal liver metastases

Systemic FU/LV \textit{versus} SIRT + FU/LV

<table>
<thead>
<tr>
<th>Survival</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>12.8 months</td>
</tr>
<tr>
<td>SIRT + Chemotherapy</td>
<td>27.1 months</td>
</tr>
</tbody>
</table>

\textit{ASCO 2002:599}
Patient with colorectal liver metastases. Response 15 months after treatment with SIR-Spheres + 5FU/LV
Patient with colorectal liver metastases. Response 10 months after treatment with SIR-Spheres + 5FU/LV.
Down-staging Advanced Liver Cancer to Resectability
C/R mets: R lobe only
 treated CT Scan before/after SIRT
C/R mets: R lobe only treated
PET Scan before/after SIRT
SIRT complements Surgery & Chemotherapy

SIRT increases surgical options
SIRT increases chemotherapy
Other Cancers

SIRT is targeted radiotherapy and therefore will have effect in all cancers
The APUD/NEUROENDOCRINE CELL CONCEPT

Dispersed Neuroendocrine Cells With Somatostatin Receptors

Source: Lamberts SW), et al. Trends in Endocrinal Metab. 1990, (Jan./Feb.): 139-144.
R hepatic artery CT scan – Pancreas Cancer Liver Mets
Primary HCC
SIR-Spheres in HCC

71 Patients with advanced HCC

- 89% a-Fetoprotein Response
  (22% CR  67% PR)
- 27% Tumour Volume Response

W Lau, S Ho, T Leung, M Chan, R Ho, P Johnson, A Li:
Serum Alpha-fetoprotein following treatment with SIR-Spheres

W Lau, S Ho, T Leung, M Chan, R Ho, P Johnson, A Li:
SIR-Spheres in HCC

71 Patients with advanced HCC

- 5% of patients were down-staged to become resectable.
- Only 15-30 Gy mean dose can be delivered.
- Dose limited by flow stasis

Theraspheres in HCC

• Y-90 Theraspheres have higher specific activity – smaller number of particles.
• Higher doses can be delivered (50-500 Gy).
• Clinical trials show a 50% response rate for HCC compared with our 33% with SIR Spheres.
• Longer period of tumor regression
Theraspheres in HCC

- Patients with Stage T1 or T2 eligible for liver transplant.
- 10% recurrence of tumor after transplant (90% cure).
- Of 35 patients with stage T3 HCC, who received Theraspheres, 19/35 (56%) were downstaged to T2 and became eligible for liver transplant.
- Of those, 11 actually underwent liver transplant.

(Kulik and Salem et al. J Surg Oncol 2006)
Dangers of SIRT

• GI ulceration
• Radiation pneumonitis
• Pancreatitis
• Radiation hepatitis
Lung Tolerance

• 3 of 5 patients with >30Gy total lung dose developed radiation pneumonitis
• No patient receiving <30Gy developed pneumonitis
• Animal studies of 30-33Gy showed little histologic damage
# Lung Shunting

<table>
<thead>
<tr>
<th>Activity administered (GBq)</th>
<th>Lung shunting (%)</th>
<th>Lung radiation dose (Gray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%</td>
<td>5</td>
</tr>
<tr>
<td>1.5</td>
<td>10%</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>10%</td>
<td>10</td>
</tr>
<tr>
<td>2.5</td>
<td>10%</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>10%</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>15%</td>
<td>7.5</td>
</tr>
<tr>
<td>1.5</td>
<td>15%</td>
<td>11.25</td>
</tr>
<tr>
<td>2</td>
<td>15%</td>
<td>15</td>
</tr>
<tr>
<td>2.5</td>
<td>15%</td>
<td>18.75</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>22.5</td>
</tr>
<tr>
<td>1</td>
<td>20%</td>
<td>10</td>
</tr>
<tr>
<td>1.5</td>
<td>20%</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
<td>20</td>
</tr>
<tr>
<td>2.5</td>
<td>20%</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>30</td>
</tr>
</tbody>
</table>
Liver Tolerance and Dosimetry

- External beam 40Gy has 50% probability of significant complications
- SIRT: 86% of cells get < mean liver dose and 33% get less than 30% of the dose
- Dose escalation in 10 patients showed that up to 138Gy did not cause clinical radiation hepatitis (Gray et al J Surg Oncol 1989)
- Biopsies in 4 patients receiving up to 75Gy has minimal histologic effect in healthy liver (Gray et al)
- 70Gy is tolerable in cirrhosis (Lau et al)
SIRT Dosimetry

- SIR-Spheres go where the arterial blood goes
- SIRT is point source radiation - not homogeneous radiation
- The liver size has a small effect on effect on liver radiation
- Blood flow has a large effect on normal liver radiation dose
- Blood flow has a large effect on tumour radiation dose
- The rim of tumours is always hyper-vascular
- The centre of tumours is hypo-vascular
- Small tumours are more vascular than large tumours
- Large tumour mass gets more blood flow than small tumour mass
Radiation Safety

- **Exposure**
  - Bremsstrahlung is typically 15 uSv per Gbq at 15cm from the patient’s right side (initially)

- **Precautions**
  - Non pregnant nursing staff /visitors
  - 1 foot distance from patient’s side for 3-5 days
  - Efficiency in patient observations
  - Nursing from left hand side of patient
  - Shielding unnecessary