Selective Internal Radio-Therapy (SIRT) or Trans-Arterial Radio-Embolization (TARE)

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University of Pisa, Pisa, Italy

Parnu (Estonia), October 6 – 11, 2014
SIRT – TARE

• Use of non-absorbable radioactive microspheres for pre-capillary arterial embolization of vessels supplying primary or secondary liver cancers.

• Therapeutic effect due to delivery of highly focused local radiation in the form of high energy $\beta^-$ particles.

• Multidisciplinary team including the referring oncologist (patients’ selection), the interventional radiologist (selective or superselective arterial administration), the nuclear physician (handling of radiopharmaceuticals, hybrid imaging), and the medical physicist (radiodosimetry estimates).
The Clinical Context of SIRT
Current Options for Liver Cancers

- Tumor board
- Stereotactic Radiation
- Chemotherapy
- Microwave Ablation
- CTX Perfusion
- SIRT
- Embolisation
- TACE
- RFA
- PEI
- Resection
- Nano Knife

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Effective Radioembolization for Treatment of Liver Cancers

Embolizing microspheres (20 – 60 µm diameter) are the vehicle of the β⁻ emitting radionuclide (⁹⁰Y) inducing the therapeutic effect.
Distribution Patterns of Microspheres According to Diameter

Particles

500 μm

300 μm

100 μm

35 μm

Sangro B. Journal of Hepatology 2012 vol. 56 j 464–473
Kennedy A. Radioembolization of hepatic tumors. J Gastrointest Oncol. 2014.
Kennedy A. Radioembolization of hepatic tumors. J Gastrointest Oncol. 2014.
The Radionuclide – Yttrium-90 (\(^{90}\text{Y}\))

- Physical half-life: 64.1 hours.
- Main emission: \(\beta^-\) particles with 0.93 MeV mean energy
  - 11 mm maximum range in tissue
  - \(~5.3\) mm mean range
  - 90% energy deposition within \(~2.5\) mm
- Minor emission: \(\beta^+\) particles.

<table>
<thead>
<tr>
<th></th>
<th>TheraSphere</th>
<th>SIR-Spheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>MDS-Nordion, Canada</td>
<td>Sirtex-Medical, Australia</td>
</tr>
<tr>
<td>Material</td>
<td>Glass</td>
<td>Resin</td>
</tr>
<tr>
<td>Diameter</td>
<td>20 – 40 µm</td>
<td>20 – 60 µm</td>
</tr>
<tr>
<td>Activity per particle</td>
<td>2500 Bq</td>
<td>50 Bq</td>
</tr>
<tr>
<td>Supplied activity vials</td>
<td>3, 5, 7, 10, 15, 20 GBq</td>
<td>3, 6 GBq</td>
</tr>
<tr>
<td>Number of microspheres</td>
<td>1, 2, 3, 4, 6, 8 (\times) (10^6)</td>
<td>(~40, ~80 \times 10^6)</td>
</tr>
<tr>
<td>Preparation of dose</td>
<td>Radioactive decay</td>
<td>Manual calibration</td>
</tr>
<tr>
<td>Embolizing effect</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Liver Tolerance and Tumor Sensitivity

RILD – Radiation-Induced Liver Disease

Curative Doses: Adenocarcinoma

Preoperative Radiation: Rectal Ca.

SIRT – Tissue Sensitivity to Radiation and Oxygenation Level

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SIRT – Radiation Dosimetry

<25 Gy

> 120 Gy

> 120 Gy

Micro dosimetrie Explantat

1000 Gy Dose Volume
**SIRT – Clinical Aspects**

**Indications:**

- Metastasized colorectal carcinoma (mCRC); first, second or third line, salvage therapy.

- Unresectable hepato- or cholangiocellular carcinoma (HCC / CCC).

- Neuroendocrine liver metastasis.
SIRT – Patient Selection

Official guidelines:
• Live expectancy of at least 4 months
• Not pregnant
• No systemic chemotherapy within 4 weeks
• No prior radiotherapy to the liver

Contraindications:
• Ascites or signs of liver failure (Bilirubin >2 mg/dL)
• Child score >B
• \((\text{Tumor volume})/\text{(Liver volume)}\) ≤0.5
• High extra-hepatic tumor burden
• Renal failure
• Excessive shunting to the lungs (>20%)
• Reflux to gastrointestinal tract arteries
SIRT – Multistep Procedure

1. Initial work-up for selection of candidates to treatment.

1. Preparation of the arterial vasculature and measurement of liver volumes.

1. Pre-treatment evaluation of liver pulmonary shunts and/or abnormal reflux.

1. Radiation dosimetry estimates.

1. Infusion of $^{90}$Y-particles and assessment of their distribution.

1. Follow-up.
**SIRT – Simplified Dose Calculation**

Activity (GBq) = (BSA – 0.2) + Tumor Volume/(Overall Volume)

<table>
<thead>
<tr>
<th>Liver Volume</th>
<th>1600</th>
<th>1000</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Volume</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Dose GBq (mCi)</td>
<td>1.7275 (46.7)</td>
<td>1.84 (49.7)</td>
<td>2.14 (57.8)</td>
</tr>
</tbody>
</table>

Caution with small livers, especially after chemotherapy
- Risk of RILD -

Need for establishing more precise dosimetry models


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Image-Guided Personalized Predictive Dosimetry by Artery-Specific SPECT/CT Partition Modeling for Safe and Effective $^{90}$Y Radioembolization

Yung Hsiang Kao$^1$, Andrew Eik Hock Tan$^1$, Mark Christiaan Burgmans$^2$, Farah Gillian Irani$^2$, Li Ser Khoo$^2$, Richard Hoau Gong Lo$^2$, Kiang Hiong Tay$^2$, Bien Soo Tan$^2$, Pierce Kah Hoe Chow$^{3,4}$, David Chee Eng Ng$^1$, and Anthony Soon Whatt Goh$^1$

$^1$Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore; $^2$Department of Diagnostic Radiology, Singapore General Hospital, Singapore; $^3$Department of General Surgery, Singapore General Hospital, Singapore; and $^4$Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

DOI: 10.2967/jnumed.111.097469
FIGURE 1. Example of artery-specific SPECT/CT partition modeling of 3 arterial territories. (A–C) Liver with multifocal HCC supplied by right (A), middle (B), and left (C) hepatic arteries is depicted in digital subtraction angiography (top) and catheter-directed CTHA (bottom). (D) Regions of interest (ROI) are drawn on $^{99m}$Tc-MAA SPECT/CT transaxial slices representing left (blue ROI), middle (orange ROI), and right (green ROI) hepatic artery planning target volumes, implanted tumor (red ROI), and necrotic tumor (white ROI).
SIRT – Multiple Roles of Imaging

Pre-selection

CT/MR, PET/CT

Selection

Angio
SPECT/CT

Exclusion

Dosimetry

CT/MR, SPECT/CT (PET/CT)

Treatment

$^{90}$Y-PET/CT

Follow-up

CT/MR, PET/CT
SIRT – Patient Preparation

- Identification by angio all arteries supplying the tumor lesions.
- Plan position of the catheter so as to include all the tumor lesion(s) and exclude healthy parenchyma.
- Identify extrahepatic branches and embolize.
- Administer $^{99m}$TC-MAA and acquire planar and SPECT/CT imaging within 1 hour.
- Exclude liver $\rightarrow$ lung shunt >20%.
SIRT – Selective/Superselective Infusion

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*Sangro B. Journal of Hepatology 2012 vol. 56 j 464–473*
SIRT – $^{99m}$Tc-MAA

Liver ➔ lung shunt = 29%
SIRT – $^{99m}\text{Tc}$-MAA

Reflux to cholecystic artery: embolize before further attempt
SIRT – $^{99m}$Tc-MAA

Reflux to abdominal wall: embolize before further attempt
Activity Calculator

Date: Auto Generated          User reference: 

Patient Data

Patient height: 

Total liver volume (cc/cm³):

Patient weight: 

Target Region

Volume of liver to be treated (cc/cm³):

Volume of tumour in treated region (cc/cm³):

Lung Shunt

Lung shunt (%):

Estimated lung mass:

Calculated activity (GBq):

Activity reduction (%):

Activity after reduction (GBq):

Sirtex Medical Limited
Level 33, 101 Miller Street
North Sydney NSW 2060
Australia
+61 2 9964 8400,
SIRT – Infusion of $^{90}$Y-Microspheres
SIRT – Infusion of $^{90}$Y-Microspheres
Bremsstrahlung SPECT/CT

$^{90}$Y-PET/CT
**90Y SIRT: Therapy control scan**

- **90Y-Bremsstrahlen SPECT/CT:**
  - + Cheap, available
  - - Low resolution
  - - not quantitative

- **90Y PET/CT:**
  - + higher spatial resolution
  - + quantitative images
  - - Higher costs

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Lhomme et al, EJNMMI 2009; 36: 1696
Gates et al, JNM 2011;52:72-76
**90Y SIRT: Therapy control scan**

The gain in resolution should increase the accuracy of the dose distribution calculations of tumors and surrounding tissues.

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*99mTc-MAA SPECT/CT scan*  
*90Y PET/MR scan*

*Courtesy of Dr. Michael Wissmeyer, HUG Switzerland*

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# SIRT: side effects - risks

<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 onset on Tx day for up to 1 week</td>
<td>normally none 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>Nausea</td>
<td>~40%</td>
<td>highest in Tx-experienced; normally &lt;24 h</td>
<td>prophylactic anti-emetics</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>Abnormal LFTs</td>
<td>~20–40%</td>
<td>particularly in combination transient; resolves in days (ALT, AST), weeks (bilirubin) or months (alb.)</td>
<td>none normally</td>
</tr>
</tbody>
</table>
## SIRT: side effects - risks

<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% 1–2% grade 3–4</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 dose; dose reduction in patients with reduced hepatic reserve</td>
</tr>
</tbody>
</table>
\textbf{99mTc-MAA} \\
\textbf{90Y-PET/CT} \\
\textbf{90Y-Bremsstrahlung SPECT/CT}
Pre-treatment

97.916 cm³

4 months post-treatment

10.423 cm³
Clarck ME, Smith RR. Liver-directed therapies in metastatic colorectal cancer. *J Gastrointest Oncol.* Oct 2014; 5: 374-387

• The response rates are 12.9-35.5%, with 24-65% achieving stable disease.

• The median OS following $^{90}$Y is 10.2-12.6 months.

• This is achieved in patients who have failed all lines of chemotherapy.

Trans-arterial treatment of liver malignancies with RE is an emerging treatment modality. RE is predominantly performed in patients with no curative options, mostly in a salvage setting. Potentially curative settings in which RE may be applied include downstaging patients to resec disease, a bridge to transplantation and induction of remnant liver hypertrophy. RE involves a combination of tumor reduction and disease control, minimizing the chance of tumor progression during the time interval prior to liver surgery with curative intent. This may eventually lead to prolonged survival, although prospective controlled trials are needed to test this hypothesis. Imaging is indispensable for patient selection and dosimetry-based treatment planning to use the full potential that RE has to offer in patients with liver malignancy, especially when liver surgery with curative intent might still be an option.

First-Line for HCC: SIRT versus Supportive Care

Control group: 43 ± 8 months
SIR-Spheres microspheres: 35 ± 16 months

Median Survival

\[ P < 0.001 \]

Actuarial Survival

LIVER METASTASES FROM NEUROENDOCRINE TUMORS:
• Commonly high arterial perfusion
• Overall better response rate compared to TACE or chemotherapy.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>n</th>
<th>ORR</th>
<th>SD</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1st-line to treatment-refractory disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennedy</td>
<td>148‡</td>
<td>63.2%</td>
<td>22.7%</td>
<td>70 mo median</td>
</tr>
<tr>
<td>King</td>
<td>34</td>
<td>50%</td>
<td>14.7%</td>
<td>59% at 35.2 mo</td>
</tr>
<tr>
<td>Saxena</td>
<td>48</td>
<td>54%</td>
<td>23%</td>
<td>35 mo</td>
</tr>
<tr>
<td>Cao</td>
<td>58‡</td>
<td>39.2%</td>
<td>27.4%</td>
<td>36 mo</td>
</tr>
<tr>
<td>Meranze</td>
<td>10</td>
<td>40%</td>
<td>60%</td>
<td>70% at 28 mo</td>
</tr>
<tr>
<td>Jakobs</td>
<td>25‡</td>
<td>20.8%</td>
<td>75%</td>
<td>96% at 12 mo</td>
</tr>
</tbody>
</table>

*Kennedy et al, Am J Clin Oncol 2008;31:271-9*
mNET: SIRT versus TACE

Only one retrospective trial with 46 patients with NET (G1/G2) – 19 SIRT patients versus 27 TACE patients

<table>
<thead>
<tr>
<th></th>
<th>SIRT:</th>
<th>TACE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>PR</td>
<td>51%</td>
<td>59%</td>
</tr>
<tr>
<td>SD</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>PD</td>
<td>8%</td>
<td>21%</td>
</tr>
</tbody>
</table>

PFS: SIRT 44 months versus TACE 12 months (p = 0.015)

Both therapies were well tolerated without significant difference in overall survival after a follow up of 104 months.

Yuhsin V. Wu et al. J Clin Oncol 30, 2012 (4;300)
Primary SIRT therapy with 1.7 GBq (45.9 mCi), ambulant
Partial response over 16 months, scheduled for 2nd therapy now

Irene Burger
The FOXFIRE Global Study

*SIR-Spheres®* + FOLFOX *versus* FOLFOX Alone

(with or without bevacizumab) in Patients with Unresectable Liver Metastases from Colorectal Cancer

**Schema:**
- **Stratify**
  - Presence of extra-hepatic metastases
  - Degree of liver involvement
  - Institution
  - Use of bevacizumab
- **Randomise**
  - 1:1
  - n=200–300

**FOLFOX6m** ± bevacizumab

*4, 5*

*Oxaliplatin administered at 60 mg/m2 for 6 weeks in the test arm, starting 3–4 days prior to the SIR-Spheres microspheres administration.*

*4, 5* At the investigators discretion and relative to the SIR-Spheres microspheres administration date, bevacizumab may commence at Cycle 4 or 5 in the test arm and at cycle 1 in the control arm.

*SIR-Spheres®* is a registered trademark of Sirtx SIR-Spheres Pty Ltd
FIRST LINE:

• Liver dominant or liver only metastasized colorectal cancer: First line FOLFOX vs SIRT/FOLFOX or 5FU
• 5 studies with overall over 100 patients
• significant increase of overall survival for FOLFOX/SIRT.
  • FOLFOX 16 – 19 months
  • SIRT/FOLFOX 29 – 38 months

First line mCRC: SIRT/5FU vs 5/FU

- **5FU/LV + SIR-Spheres**: 29.4 months
- **5FU/LV**: 12.8 months

Hazard Ratio 0.33 (95% CI 0.12–0.91)  
$P = 0.025$

Eligible Patients:
- Unresectable liver-only or liver-predominant metastatic CRC
- No prior chemotherapy for mCRC
- Fit for combination therapy and SIRT

Stratify:
- Presence of extra-hepatic metastases
- Degree of liver involvement
- Institution
- Use of bevacizumab

Secondary endpoints:
- PFS in liver
- Overall survival
- Response rate
- Quality of life
- Recurrence rate
- Toxicity and safety

Primary endpoint: Progression-free survival (PFS)
Sponsor: Sirtex
PIs: Prof. Peter Gibbs; Prof. Guy van Hazel
Status: Enrolment complete (March 2013)

Results expected at the next ASCO Meeting
SIRT – Conclusion

Potential technical improvements:
- Adequate activity administration
- Patient selection – predicting response with perfusion CT
- Vascular redistribution – reducing SIRT interventions
- Improved therapy control with $^{90}\text{Y}$-PET

Clinical outcome:
- Promising results have been published, especially for mCRC, HCC and CCC.
- The large multicenter trials SIRveNIB, SIRFLOX and SIR-KRAS closed in 2013. Results will be presented at the ASCO Meeting in 2015.