Selective Internal RadioTherapy

Irene A. Burger, MD
Pärnu (Estonia), October 6 – 10, 2014

Radiology and Nuclear Medicine Department
University Hospital Zurich
Switzerland
Y-90 Radioembolization of the liver

- Yttrium-90 radiotherapy was investigated for cancer therapy since the 1960s
- 1977 first publications for internal radioembolization of liver metastasis in humans (Grady et al)
### SIRT – technical aspects:

<table>
<thead>
<tr>
<th>Material</th>
<th><strong>Resin</strong></th>
<th><strong>Glass</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>SIR-Spheres</td>
<td>Theraspheres</td>
</tr>
<tr>
<td>Manufacturer and location</td>
<td>Sirtex Medical, Lane Cove, Australia</td>
<td>MDS Nordion, Kanata, Canada</td>
</tr>
<tr>
<td>Diameter</td>
<td>20-60 µm</td>
<td>20-30 µm</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.6 g/dL</td>
<td>3.6 g/dL</td>
</tr>
<tr>
<td>Activity per particle</td>
<td>50 Bq/1.4 nCi</td>
<td>2500 Bq/67.6 nCi</td>
</tr>
<tr>
<td>Number of microspheres per 3 GBq vial</td>
<td>40-80 million</td>
<td>1.2 million</td>
</tr>
<tr>
<td>Material</td>
<td>resin with bound yttrium</td>
<td>glass with yttrium in matrix</td>
</tr>
</tbody>
</table>
Y-90 Radioembolization of the liver

Step 1 – Imaging and Planning
- FDG-PET/CT
- Tc MAA Scan

Step 2 – Therapy
- Therapy with 90-Yttrium Spheres

Step 3 – Control
- Control with Bremstrahlen Scan
Y-90 SIRT: Principle mechanism

Afferent
- Pfortader
- A. Hepatica
  - Normal 80%
  - Tumor minimal
  - Normal 20%
  - Tumor ~100%

O2 ↓

O2 ↑
Liver tolerance & tumor sensitivity

RILD – Radiation-Induced Liver Disease

Curative Doses: Adenocarcinoma

Preoperative Radiation: Rectal Ca

Gy: 20  30  40  50  60  70  80  90  100

Y-90 SIRT: Principle mechanism

<25Gy

> 120 Gy

> 120 Gy

1000 Gy Dose Volume
Y-90 SIRT: Clinical set up
SIRT - overview:

New technical aspects:
• Patient work up
• Patient selection
• Vascular redistribution
• Radiation exposure of the interventional team

Clinical outcome data:
• Metastasized colorectal carcinoma
• Unresectable hepatoo- or cholangiocellular carcinoma
• Neuroendocrine liver metastasis
Patient work up:

- Dose calculation: using MRI or ceCT volumetry
- Diagnostic angiography with embolization of gastrointestinal vessels
- MAA-hepatic angiography for detection of reflux, pulmonary shunt
- Optional FDG PET/CT: extrahepatic disease & extent of metabolic active liver disease
Y-90 SIRT: Dose calculation

\[ Dose \ (GBq) = (BSA \ (m^2) - 0.2) + \frac{Tumor \ Volume}{Tumor \ & \ Liver \ Volume} \]

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

Caution with small livers esp. after chemotherapy
- RILD -
we have to establish more precise models for dosimetry

Giammarile et al. EANM Guidelines, EJNMMI 2011;38:1393-1406
Patient selection:

Official guidelines:
• Live expectancy of at least 4 months
• Not pregnant

Relative contraindications:
• Ascites or signs of liver failure (Bilirubin > 2.0 mg/dl)
• Child score > B
• High extra-hepatic tumor burden
• Renal failure
• Excessive shunting to the lungs (> 20%)
• Previous radiotherapy to the liver
Patient selection:

With selection of patients that will respond well the outcome of SIRT could be improved.

Tumors with high arterial perfusion should have a better response than lesions with low arterial enhancement.
Patient selection: Can we predict outcome?

38 patients underwent FDG PET/CT and perfusion ceCT prior to SIRT:

- Liver metastasis on ceCT
- High arterial perfusion with 45.2 /100 ml/min
- Also on angiography the lesions are hypervascular
- CT 134 days after SIRT – significant reduction in size

*Morsbach et al, Investigative Radiology 2013;48:787-794*
Patient selection: Can we predict outcome?

Other patients with low arterial perfusion (e.g. 8.9/100 ml/min) showed no reduction in tumor size.

Significant correlation of arterial perfusion and responders vs non responders to SIRT:

Morsbach et al, Investigative Radiology 2013;48:787-794
Patient selection: Can we predict outcome?

There was a correlation between arterial tumor perfusion and relative tumor size reduction.

There was also an association between high arterial perfusion prior to SIRT and overall survival ($p = 0.028$).

Morsbach et al, Investigative Radiology 2013;48:787-794
Patient selection: Can we predict outcome?

Higher correlation between response and arterial tumor perfusion compared to other ceCT or $^{99m}$TC-MAA parameters:

- **AUC**
  - Art. Perfusion: **0.971*** (p<0.001)
  - Art. HU: **0.866*** (p=0.001)
  - Port.V. HU: 0.796
  - MAA ratio: 0.402

*Morsbach et al, European Radiology 2014;24:1455-1465*
Patient selection: vascular redistribution

“Radioembolization of Hepatic Tumors: Flow Redistribution After the Occlusion of Intrahepatic Arteries.”

To avoid multiple SIRT injections occlusion of segmental hepatic arteries => A flow redistribution through intrahepatic collaterals.

- In 24 of 27 (89%) patients with HCC or liver metastasis sufficient vascular redistribution after occlusion of Seg II/III or Seg IV artery could be observed.
  - In 16 patients flow redistribution could be shown on subsequent MAA scans.
  - In 8 patients redistribution was observed on therapy angiography after mean 16 days (range 11-26).

Lauenstein et al, Röfo 2011;183: 1058-1064
Patient selection: vascular redistribution

Vascular redistribution can be helpful for:
- Therapy of segments that are supplied by aberrant arteries
- Therapy of patients with vascular variants
- Therapy of lesions in different segments without changing catheter position

Lauenstein et al, Röfo 2011;183: 1058-1064
Radiation exposure to staff:

• SIRT therapy with $^{90}$-Y causes exposure to high energy $\beta^-$ radiation if not shielded with acrylic glass:
Radiation exposure to staff:

- Extension of acrylic glass coverage to protect the hands of the interventional physician:
Radiation exposure to staff:

- Preliminary results showed a reduction of radiation exposure of about 60% with additional acrylic glass protection:
Y-90 SIRT: Therapy control scan

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

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

---

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

The gain in resolution should increase the accuracy of the dose distribution calculations of tumors and surrounding tissues.
SIRT – clinical context:

cancer treatment today

Nuclear Medicine

Intervent. Radiology

Radiation Oncology

Medical Oncology

Hepatology

Surgery
SIRT – current options:

- Stereotactic Radiation
- Chemotherapy
- Microwave Ablation
- CTX Perfusion
- PEI
- Nano Knife
- Resection
- RFA
- TACE
- Embolisation
## 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></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 1\textsuperscript{st} 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>
# 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%</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 gastritis or duodenitis</td>
<td>1–2% grade 3–4</td>
<td></td>
<td></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;</td>
<td>appropriate dose; dose reduction in patients with reduced hepatic reserve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>permanently elevated LFTs, portal hypertension, eventual fibrosis</td>
<td></td>
</tr>
</tbody>
</table>
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
RESULTS – STUDIES
METASTASIZED COLORECTAL CARCINOMA (mCRC)
SIRT – clinical outcome: mCRC

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

- n = 21
- Median Survival
  - 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

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

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

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

Randomise 1:1
n ≥ 450

Multiple SIRTEX Studies completed: e.g.

Results expected next ASCOM meeting.
SIRT – clinical outcome: mCRC

SECOND or THIRD LINE:
• Limited data
• 2 studies with overall over 50 patients
• significant increase of overall survival for FOLFOX/SIRT.
  • 2\textsuperscript{nd} Irinotecan 6 - 10 months
  • 3\textsuperscript{rd} Panitumumab 8 - 10 months
  • SIRT/Irinotecan 12 - 17 months

SIRT – clinical outcome: mCRC

Salvage therapy:
- Best data available
- Over 12 studies with up to 600 patients, overall over 1300 patients
- Significant increase of overall survival for SIRT compared to historical controls of non responders.
  - SIRT 10 - 14 months
  - Historical controls 5 - 7 months

mCRC: rectal cancer therapy refractory

ceCT scan - pre

$^{99m}$Tc-MAA scan

$^{90}$Y SPECT

ceCT perfusion scan 4 weeks later

Nuclear Medicine, University Hospital Zurich
Baseline ceCT scan pre-SIRT

90Y Injection & SPECT

ceCT scan 2 months post-SIRT
SIRT – clinical outcome: HCC

FIRST LINE:
- Patients with unresectable HCC
- 2 studies with overall over 70 patients
- significant increase of overall survival for SIRT.
  - Supportive care / active therapy  8 months
  - SIRT  14- 16 months

First line HCC: SIRT/Supportive care

- Control group: 43 patients, 8 months median survival
- SIR-Spheres microspheres: 35 patients, 16 months median survival

\[ P < 0.001 \]

72 yo man with recurrent HCC

A total of 5 lesions: all with very high arterial perfusion.

SIRT: 1.6 GBq/43.2 mCi (right liver)

CT follow up after 4 we and 6 months
SIRT – clinical outcome: HCC

FIRST- or SECOND LINE to ADVANCED DISEASE:

- Patients with unresectable HCC, not suitable for liver transplant.
- 8 studies with overall over 700 patients
- Significant increase of overall survival for SIRT for patients with advanced HCC:
  - Placebo: 7.9 months
  - Sorafenib: 10.7 months
  - SIRT: 14-16 months

Sangro et al, Am J Clin Oncol 2011;34:422-431
68 Yo woman with recurrent HCC

2 months later SIRT II: 0.8 GBq/21.6 mCi (Seg VII)

SIRT I: 1.2 GBq/32.4 mCi (Seg IV)

MRI 5 months after 2. injection.
RESULTS – STUDIES
COLANGIOCELLULAR CARCINOMA
SIRT – clinical outcome: CCC

AGRESSIVE, CHEMO-REFRACTORY DISEASE:
• 8 studies with overall over 100 patients
• Prospective study with unresectable patients that failed chemotherapy:
  • 24% response rate (RECIST)
  • 48% stable disease (RECIST)

Saxena et al, Ann Surg Oncol 2010; 17:484-491
48 yo with CCC

FDG PET/CT before SIRT
Dynamic ceCT before SIRT
MRI 8 weeks after SIRT
Dynamic ceCT 6 weeks after SIRT
48 yo with CCC

Follow up MRI 36 months post Therapy:
no evidence of recurrence
34 yo with CCC: SIRT with Cis/Gemzar
34 yo with CCC: R0 resection

MRI 5 months post therapy no evidence for recurrence
RESULTS – STUDIES
NEUROENDOCRINE LIVERMETASTASIS
SIRT – clinical outcome: NET

LIVERMETASTASES 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>

mNET: SIRT vs TACE

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

SIRT:  26% CR  51% PR  15% SD  8% PD
TACE:  13% CR  59% PR  8% SD  21% PD

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)
39 yo woman, pancreatic NET

(G2 16% MIB, N0, M1 (hep))

Primary SIRT therapy with 1.7 GBq/45.9 mCi, ambulant
Partial response over 16 months, scheduled for 2nd therapy now

Pre-SIRT:

4 we - ceCT

6 mo – FDG PET
SIRT – Conclusion:

Potential technical improvements:
- Adequate dose administration
- Patient selection – predicting response with perfusion CT
- Vascular redistribution – reducing SIRT interventions
- Improved Therapy control with $^{90}$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 2013. Results will be presented at ASCOM 2015.
Thank you!