SIRT in Neuroendocrine Tumors

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Disclosure of speaker’s interests

Consultant for BTG, Terumo and Sirtex
Advisor for Bayer Healthcare

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Radioembolization
<table>
<thead>
<tr>
<th>Microsphere specifications</th>
<th>TheraSphere®</th>
<th>SIR-Spheres®</th>
<th>Quiremspheres®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radionuclide (T½ in hours)</td>
<td>$^{90}\text{Y}$ (64.1)</td>
<td>$^{90}\text{Y}$ (64.1)</td>
<td>$^{166}\text{Ho}$ (26.8)</td>
</tr>
<tr>
<td>$E_{\beta_{\text{max}}}$ in MeV</td>
<td>2.28 (99.9%)</td>
<td>2.28 (99.9%)</td>
<td>1.85 (&gt;90%)</td>
</tr>
<tr>
<td>$E_y$ in keV</td>
<td>2x 511 (&lt;0.1%)</td>
<td>2x 511 (&lt;0.1%)</td>
<td>81 keV (6.8%)</td>
</tr>
<tr>
<td>Microsphere material</td>
<td>Glass</td>
<td>Resin</td>
<td>Polylactic acid</td>
</tr>
<tr>
<td>Relative embolic effect</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Number of particles</td>
<td>5 million</td>
<td>50 million</td>
<td>30 million</td>
</tr>
<tr>
<td>Specific activity (Bq/microsphere)</td>
<td>1.250 – 2.500</td>
<td>50</td>
<td>330 – 450</td>
</tr>
<tr>
<td>Scout dose</td>
<td>$^{99m}\text{Tc-MAA}$</td>
<td>$^{99m}\text{Tc-MAA}$</td>
<td>$^{166}\text{Ho}$-MS</td>
</tr>
<tr>
<td>Contrast injection during infusion</td>
<td>Possible</td>
<td>Only alternately</td>
<td>Possible</td>
</tr>
<tr>
<td>Imaging modality</td>
<td>SPECT or PET</td>
<td>SPECT or PET</td>
<td>SPECT or MRI</td>
</tr>
</tbody>
</table>
Growing interest in radioembolization: mCRC

Systemic treatment for colorectal cancer patients with liver-dominant metastases

1st line
fluoropyrimidine based regimen + bevacizumab ± oxaliplatin / irinotecan
progression / toxicity

2nd line
irinotecan or oxaliplatin based regimen
progression / toxicity

3rd line
Anti-EGFR treatment (cetuximab or panitumumab)
progression / toxicity

INVESTIGATIONAL USE
radioembolization
radioembolization
radioembolization
radioembolization

Kras wild type?
no (60%)
yes (40%)

upward trend

References
1. FOXFIRE study, Sharma et al., Clin Oncol 2008; 20: 261-3
2. SIRFLOX study, www.sirfox.com
3. SIR-step trial, clinicaltrials.gov: NCT01895257
4. inSIRT study, Reid et al., JVIR 2012; WCIO abstracts poster 42
5. EPOCH study, clinicaltrials.gov: NCT01483027
7. Cosimelli et al., Br J Cancer, 2010; 103: 324-31

Braat et al. JNM 2015
Growing interest in radioembolization: HCC

**Hepatocellular carcinoma (HCC)**

- **Very early + early (BCLC 0 & A)**
  - Resection
  - Liver transplantation
  - Radiofrequency ablation
- **Intermediate + advanced (BCLC B - C)**
  - Radioembolization
  - Chemoembolization
  - Sorafenib
- **Terminal (BCLC D)**
  - Best supportive care

**Treatment**

- **Resection**
  - Solitary tumor
  - Milan criteria
- **Radiofrequency ablation**
  - Underlying liver disease
- **Chemoembolization**
  - Performance score 0 without portal vein thrombus
  - <5 tumors
  - HCC < 10 cm
- **Radioembolization**
  - Performance score ≤ 2
  - +/- portal vein thrombus
  - Multifocal disease
  - Tumor size > 5 cm
  - Limited extrahepatic spread
- **Sorafenib**
  - Performance score ≤ 2
  - Child-Pugh B8-9
  - Extrahepatic spread
  - Ineligible for TACE/RE
- **Best supportive care**
  - Performance score > 2 and/or
  - Child-Pugh C

**criteria**

- Performance score ≤ 2
- Child-Pugh B8-9
- Extrahepatic spread
- Ineligible for TACE/RE

**Survival**

- >70%
- 5-years survival
- 20 months
- 13-18 months
- 6-13 months
- <3 months

Braat et al. JNM 2015
Treatment mNET

mNET patients (liver-only or liver-predominant disease)

- Treat endocrine and other symptoms
  - somatostatin analogue (carcinoid);
    proton pump inhibitor (gastrinoma);
    diazoxide (Insulinoma), etc.

  - Curative or palliative resection /ablation

  - Yes: Amenable to resection/ablation

  - No: Physician preference

  - High-grade mNETs (poorly-differentiated)
    - Systemic chemo; i.e., cisplatin + etoposide

  - Low-grade mNETs
    - Systemic chemo; i.e., streptozocin + 5FU or doxorubicin + 5FU

  - Uptake of MIBG or somatostatin analogue
    - Radionuclide Therapy; i.e., $^{177}$Lu-DOTA-octreotide

  - Functional disease
    - TAE/TACE

  - Functional or non-functional disease
    - $^{90}$Y resin microspheres

Kennedy et al. 2012
“*SIRT (selective internal radiation therapy) is still an investigational method”
Radioembolization in NET; what to expect?

The Efficacy of Hepatic $^{90}$Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis

Zlatko Devcic¹, Jarrett Rosenberg², Arthur J.A. Braat³, Tust Techasith¹, Arjun Banerjee¹, Daniel Y. Sze¹, and Marnix G.E.H. Lam¹,³

¹Division of Interventional Radiology, Stanford University School of Medicine, Stanford, California; ²Radiology Sciences Laboratory, Stanford University School of Medicine, Stanford, California; and ³Department of Radiology and Nuclear Medicine, UMC Utrecht, The Netherlands

- Objective response rate 50%
- Disease control rate 86%
- Median overall survival 28.5 months
### Efficacy yttrium-90 radioembolization in NET

#### TABLE 2
Critical Appraisal According to Research Reporting Standards for Radioembolization

<table>
<thead>
<tr>
<th>Study</th>
<th>Study year</th>
<th>Major criteria score</th>
<th>Minor criteria score</th>
<th>All criteria weighted score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy</td>
<td>2008</td>
<td>60%</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td>Paprotka</td>
<td>2011</td>
<td>83%</td>
<td>47%</td>
<td>74%</td>
</tr>
<tr>
<td>Lacin</td>
<td>2011</td>
<td>79%</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>King</td>
<td>2007</td>
<td>88%</td>
<td>59%</td>
<td>79%</td>
</tr>
<tr>
<td>Cao</td>
<td>2010</td>
<td>80%</td>
<td>28%</td>
<td>66%</td>
</tr>
<tr>
<td>Kalinowski</td>
<td>2008</td>
<td>83%</td>
<td>58%</td>
<td>76%</td>
</tr>
<tr>
<td>Rhee</td>
<td>2008</td>
<td>75%</td>
<td>42%</td>
<td>66%</td>
</tr>
<tr>
<td>Saxena</td>
<td>2010</td>
<td>92%</td>
<td>50%</td>
<td>81%</td>
</tr>
<tr>
<td>Ezzidin</td>
<td>2012</td>
<td>88%</td>
<td>58%</td>
<td>78%</td>
</tr>
<tr>
<td>Arslan</td>
<td>2011</td>
<td>88%</td>
<td>39%</td>
<td>75%</td>
</tr>
<tr>
<td>Murthy</td>
<td>2008</td>
<td>88%</td>
<td>48%</td>
<td>76%</td>
</tr>
<tr>
<td>Ozao-Choy</td>
<td>2013</td>
<td>52%</td>
<td>19%</td>
<td>42%</td>
</tr>
</tbody>
</table>

*Total score for inclusion of minor criteria and major criteria per study.

Devcic et al. JNM 2014
Efficacy of yttrium-90 radioembolization in NET

<table>
<thead>
<tr>
<th>Study</th>
<th>CR+PR</th>
<th>Procedures</th>
<th>Proportion</th>
<th>95%-CI</th>
<th>w (fixed)</th>
<th>w (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murthy (2008)</td>
<td>1</td>
<td>8</td>
<td>0.12</td>
<td>[0.00;0.53]</td>
<td>0.9%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Kalinowski (2008)</td>
<td>6</td>
<td>9</td>
<td>0.67</td>
<td>[0.30;0.93]</td>
<td>2.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Lacin (2011)</td>
<td>5</td>
<td>10</td>
<td>0.50</td>
<td>[0.19;0.81]</td>
<td>2.6%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Arslan (2011)</td>
<td>8</td>
<td>10</td>
<td>0.80</td>
<td>[0.44;0.97]</td>
<td>1.7%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Ozao-Choy (2013)</td>
<td>11</td>
<td>19</td>
<td>0.58</td>
<td>[0.33;0.80]</td>
<td>4.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Rhee (2008)</td>
<td>8</td>
<td>16</td>
<td>0.50</td>
<td>[0.25;0.75]</td>
<td>4.2%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Ezzidin (2012)</td>
<td>7</td>
<td>23</td>
<td>0.30</td>
<td>[0.13;0.53]</td>
<td>5.1%</td>
<td>8.6%</td>
</tr>
<tr>
<td>King (2007)</td>
<td>18</td>
<td>33</td>
<td>0.55</td>
<td>[0.36;0.72]</td>
<td>8.5%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Paprottka (2011)</td>
<td>9</td>
<td>40</td>
<td>0.22</td>
<td>[0.11;0.38]</td>
<td>7.3%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Saxena (2010)</td>
<td>26</td>
<td>48</td>
<td>0.54</td>
<td>[0.39;0.69]</td>
<td>12.5%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Cao (2010)</td>
<td>23</td>
<td>51</td>
<td>0.45</td>
<td>[0.31;0.60]</td>
<td>13.2%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Kennedy (2008)</td>
<td>117</td>
<td>168</td>
<td>0.70</td>
<td>[0.62;0.76]</td>
<td>37.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td><strong>Fixed effect model</strong></td>
<td>435</td>
<td></td>
<td>0.56</td>
<td>[0.51;0.60]</td>
<td>100%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td>0.50</td>
<td>[0.38;0.62]</td>
<td>--</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 74.2\%$, $T^2 = 0.3386$, $P<0.0001$
Efficacy yttrium-90 radioembolization in NET

<table>
<thead>
<tr>
<th>Study</th>
<th>CR+PR+SD</th>
<th>Procedures</th>
<th>Proportion</th>
<th>95%-CI</th>
<th>w (fixed)</th>
<th>w (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murthy (2008)</td>
<td>5</td>
<td>8</td>
<td>0.62</td>
<td>[0.24;0.91]</td>
<td>4.4%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Kalinowski (2008)</td>
<td>9</td>
<td>9</td>
<td>1.00</td>
<td>[0.66;1.00]</td>
<td>1.1%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Lacin (2011)</td>
<td>9</td>
<td>10</td>
<td>0.90</td>
<td>[0.55;1.00]</td>
<td>2.1%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Arslan (2011)</td>
<td>9</td>
<td>10</td>
<td>0.90</td>
<td>[0.55;1.00]</td>
<td>2.1%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Ozao-Choy (2013)</td>
<td>17</td>
<td>19</td>
<td>0.89</td>
<td>[0.67;0.99]</td>
<td>4.2%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Rhee (2008)</td>
<td>15</td>
<td>16</td>
<td>0.94</td>
<td>[0.70;1.00]</td>
<td>2.2%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Ezzidin (2012)</td>
<td>21</td>
<td>23</td>
<td>0.91</td>
<td>[0.72;0.99]</td>
<td>4.3%</td>
<td>7.9%</td>
</tr>
<tr>
<td>King (2007)</td>
<td>23</td>
<td>33</td>
<td>0.70</td>
<td>[0.51;0.84]</td>
<td>16.3%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Paprottka (2011)</td>
<td>39</td>
<td>40</td>
<td>0.98</td>
<td>[0.87;1.00]</td>
<td>2.3%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Saxena (2010)</td>
<td>37</td>
<td>48</td>
<td>0.77</td>
<td>[0.63;0.88]</td>
<td>19.8%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Cao (2010)</td>
<td>39</td>
<td>51</td>
<td>0.76</td>
<td>[0.63;0.87]</td>
<td>21.4%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Kennedy (2008)</td>
<td>159</td>
<td>168</td>
<td>0.95</td>
<td>[0.90;0.98]</td>
<td>19.9%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

Fixed effect model: 435
Random effects model

Proportion controlled

Heterogeneity: $I^2 = 64.6\%$, $T^2 = 0.5308$, $P<0.0011$
Radioembolization in NET
Yttrium-90 glass microspheres
Radioembolization in NET
Yttrium-90 glass microspheres

$^{99m}$Tc-MAA SPECT

$^{90}$Y-PET
Radioembolization in NET
Yttrium-90 glass microspheres

Baseline
3-months
6-months
Radioembolization in NET
Holmium-166 microspheres
Radioembolization in NET
Yttrium-90 resin microspheres

Baseline

6-months
International multicenter retrospective study on efficacy and safety of radioembolization in neuroendocrine tumors with $^{90}$Y resin microspheres
# Baseline

- **244 patients = 273 procedures**

- **Grade**
  - G1: 40%
  - G2: 35%
  - G3: 10%
  - Unknown: 15%

- **Origin**
  - pNET: 35%
  - Small bowel: 35%
  - Large bowel: 9%
  - Other: 7%
  - Unknown: 14%

- **Progressive disease in 91%**

- **Tumor burden**
  - 0-25%: 30%
  - 25-50%: 29%
  - 50-75%: 35%
  - >75%: 16%

- **LSF 6.4 ± 4.4%**

- **Activity**
  - Pres.: 1.9 ± 0.6 GBq
  - Adm.: 1.8 ± 0.8 GBq

Baseline
# Efficacy

<table>
<thead>
<tr>
<th>Assessment</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;*</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;†</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;*</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response assessment</td>
<td>RECIST 1.1</td>
<td>mRECIST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median interval ± SD (days)</td>
<td>68 ± 34</td>
<td>187 ± 48</td>
<td>89 ± 78</td>
<td>189 ± 38</td>
</tr>
<tr>
<td>Number of patients</td>
<td>244</td>
<td>116</td>
<td>126</td>
<td>70</td>
</tr>
<tr>
<td>Complete response (%)</td>
<td>1.7</td>
<td>0.9</td>
<td>7.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Partial response (%)</td>
<td>14.0</td>
<td>27.6</td>
<td>34.9</td>
<td>54.3</td>
</tr>
<tr>
<td>Stable disease (%)</td>
<td>75.6</td>
<td>62.9</td>
<td>48.4</td>
<td>28.6</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>8.7</td>
<td>8.6</td>
<td>8.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Objective response rate (%)</td>
<td>15.7</td>
<td>28.5</td>
<td>42.8</td>
<td>62.9</td>
</tr>
<tr>
<td>Disease control rate (%)</td>
<td>91.3</td>
<td>91.4</td>
<td>91.3</td>
<td>91.4</td>
</tr>
</tbody>
</table>

*1<sup>st</sup> assessment around 3 months after radioembolization, †2<sup>nd</sup> assessment around 6 months after radioembolization.
Durable response

**RECIST 1.1**

- 20% improvement over time!

**mRECIST**

- 26% improvement over time!
Efficacy
Female 79-y with pNET grade 1, post-Whipple
Durable response

Baseline

3 months later

6 months later
Clinical response

- 60% had complaints prior to radioembolization
  - Flushing 43%
  - Diarrhea 40%
  - Fatigue 40%
  - Abdominal pain 35%
  - Nausea 10%

- After radioembolization
  - Improvement: 44%
  - Resolution: 35%
  - No improvement: 21%
### Toxicities within the first 3 months

**Clinical**
- **Toxicities** 56%
  - Fatigue 28%
  - Abdominal pain 27%
  - Nausea 23%
  - Vomiting 12%
  - Others <6%
- **No toxicities** 32%
- **Not reported** 12%

**Biochemical**
- **All CTCAE grades**
  - γGT 54%
  - Lymphocytopenia 21%
  - Alkaline phosphatase 5%
  - AST / ALT / bili / alb <3%
- **New grade CTCAE grade 3-4**
  - Lymphocytopenia 7%
  - Bilirubin / γGT 3%
  - ALT 2%
  - Alkaline phosphatase 1%
  - AST / alb / platelets <1%
## Complications

<table>
<thead>
<tr>
<th>Angiography</th>
<th>Radioembolization-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Arterial dissection 0.8%</td>
<td>• Radiation ulcer 2.8%</td>
</tr>
<tr>
<td></td>
<td>• REILD 0.8%</td>
</tr>
<tr>
<td></td>
<td>• Radiation pneumonitis 0.4%</td>
</tr>
<tr>
<td></td>
<td>• Abscess / cholangitis 0.4%</td>
</tr>
</tbody>
</table>
Survival

**Survival Functions**

- **Grade 1**: 3.1 years
- **Grade 2**: 2.4 years
- **Grade 3**: 0.9 years
- **Overall**: 2.6 years
Response versus survival

A. Objective response rate RECIST 1.1
B. Disease control rate RECIST 1.1

C. Objective response rate mRECIST
D. Disease control rate mRECIST

- Non-responder
- Responder
- Non-responder - censored
- Responder - censored
<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>N</th>
<th>Liver involvement</th>
<th>Median survival (months)</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain (2000)</td>
<td>Surgical resection</td>
<td>85</td>
<td>0%-25% 25%-50% 50%-75% &gt;75%</td>
<td>-</td>
<td>90% 83%</td>
</tr>
<tr>
<td>Yao (2001)</td>
<td>Surgical resection</td>
<td></td>
<td>&lt;4 liver metastases</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>Gupta (2005)</td>
<td>TAE or TACE</td>
<td>123</td>
<td>0%-25% 25%-50% 50%-75% &gt;75%</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PRRT</td>
<td>310</td>
<td>None Moderate Extensive</td>
<td>&gt;48 &gt;48 25</td>
<td>-</td>
</tr>
</tbody>
</table>

Increased liver tumor load = decreased survival
How do we improve treatment of NET patients with excessive liver disease?
Intra-arterial hepatic lutetium-177-dotatate

Gallium-68-DOTATOC PET/CT, intravenous (A) versus intra-arterial (B) administration in a patient with hypervascular liver metastasis (C). A 3.2-fold increase was observed.

Kratochwil et al. Clin Cancer Res 2010
Lutetium-177-dotatate combined with holmium-166 radioembolization

<table>
<thead>
<tr>
<th>Interval in weeks</th>
<th>200 mCi $^{177}$Lu-Dotatate</th>
<th>200 mCi $^{177}$Lu-Dotatate</th>
<th>200 mCi $^{177}$Lu-Dotatate</th>
<th>200 mCi $^{177}$Lu-Dotatate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9</td>
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Radioembolization
Non-randomized single arm phase 2 efficacy study

Boost on liver using hepatic radioembolization

HEPAR⁺

Lutetium-177-dotatate
4 x 7400 MBq

Holmium-166 radioembolization

\(^{177}\text{Lu}\)

\(^{166}\text{Ho}\)
Lutetium-177-dotatate combined with holmium-166 radioembolization
Conclusions

Liver-directed treatments may lead to overall treatment improvement in NET patients

Radioembolization in NET leads to durable responses