SIRT in the Management of Metastatic Neuroendocrine Tumors

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Disclosures

Sirtex Medical- Speaking Engagements
Bristol-Myers Squibb- Speaking Engagement
The 12 Medical Specialty Stereotypes

**ORTHOPEDICS:** The meatheads

Why no hammer/hammer? You? We hammer hard already! Need me bigger mallet!

**NEUROLOGY:** The armchair intellectual

...For you see, with the onset of herpes zoster, a polymodal nociceptive syndrome, and diminished sensation, the cutaneous branch we can isolate this to the posterior root, a lateral medullary infarct. What can you do about it now?

**EMERGENCY MEDICINE:** The cowboys

Patient's leg is bleeding! No time to call surgery! Tourniquet and amputate! Good, throw me a scalpel!

**NEUROSURGERY:** Workaholic neurosurgery

Come on people, let's get the patient in the room! Am I the only person who does work around here?

**FAMILY MEDICINE:** Hippy doctored country doctor

Now, I could give you some antibiotics for that skin infection, or I could make you a poultice of herbs.

**PSYCHIATRY:** The fake doctor

Can't you see that all of the patients with depression in his specialty lewd, sexual attraction to his childish adoring wife? Yeah, but I think he's depressed about his diabetes, being under a new control.

**DERMATOLOGY:** Giamazon.com

Immediate contagiosa is a superficial, intra-epidermal, unicellular, vesicular, viral infection.

**OB-GYN:** Overworked, bitch goddess

OK now... PUSH! PUSH! PUSH! PUSH! GOGOGOGOGO...

**RADIOLIGY:** Rich in the dark

Hey kids!! Who's ready for these shots?! Or as I like to call them, pointy objects!

**ANESTHESIOLOGY:** Sleepy bums

Geeeeeezzzz....
Neuroendocrine Tumors

- Collection of many tumor types
- Incidence increasing
- **40-95%** have liver mets at diagnosis
- Liver **#1 prognostic** factor (< 50% OS)
- Hallmark - **hypervascular** tumors
- Surgery <30% of patients (bilobar)
- **Symptoms** from paraneoplastic output
Neuroendocrine Tumors
Symptomatology

- Pain
- GI (diarrhea very common)
- Hypertension, sweating, headaches, flushing
- bloating
Concept of SIRT (Selective Internal Radiation Therapy) Radioembolization “Brachytherapy”

Treatment Goals:
Selectively deliver a tumoricidal dose of beta radiation to the liver tumor while maintaining a low radiation dose to the normal liver tissue.
$^{90}\text{Y}$ Microspheres

- Yttrium 90 layer
- Beta radiation
  - Median 2.5 mm
  - Max. 11 mm
- Tumour cells
- Normal hepatocytes
Entrapment of SIR-Spheres in Neo-vascular Bed
3D Position of $^{90}Y$ spheres

Percentage of Total Microspheres

Signed Distance from Tumor Surface (mm)
[ Distance < 0 is inside tumor]

95% $^{90}Y$ spheres near tumor masses
Recommendations for management of patients with neuroendocrine liver metastases

Andrea Frilling, Irvin M Modlin, Mark Kidd, Christopher Russell, Stefan Breitenstein, Riad Salem, Dik Kwekkeboom, Wan-yeo Lau, Catherine Klersy, Valerie Vligrain, Brian Davidson, Mark Siegler, Martyn Caplin, Enrico Solcia, Richard Schilsy, for the Working Group on Neuroendocrine Liver Metastases

Lancet Oncol 2014; 15: e8–21

- The Danish Consensus Conference model.
- 15 key questions: Diagnosis, Treatment.
- 15 groups, each multidisciplinary.
- GRADE and NCI Medical Evidence used
Where do NETs Occur and Which Types Metastasize

Figure 1: Sites of primary GEP NETs (segments) and metastases (circles)

The most common site of primary GEP NETs and metastases is the small intestine. Rectum and appendix rarely metastasise (<10%).

Appendix 20%
Small intestine 28%
Rectum 15%
Stomach 9%
Colon 13%
Pancreas 16%

Figure 2: 5 year survival for NETs (A) and gastroenteropancreatic cancers (B)
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) have a significantly better survival than adenocarcinoma at the same location. The 5 year survival of neuroendocrine liver metastases is less than 50%.1
ORIGINAL ARTICLE

Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference

Andrew Kennedy¹, Lourens Bester², Riad Salem³, Ricky A. Sharma⁴, Rowan W. Parks⁵ & Philippe Ruszniewski⁶

¹Radiation Oncology Research, Sarah Cannon Research Institute, Nashville, TN, USA, ²Department of Radiology, St Vincent’s Public Hospital, Sydney, NSW, Australia, ³Department of Radiology, Northwestern University, Chicago, IL, USA, ⁴Oncology Department, Gray Institute, University of Oxford, Churchill Hospital, Oxford, UK, ⁵Department of Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK and ⁶Centre for Gastroenterological and Pancreatic Disease, Beaujon Hospital, University of Paris Denis-Diderot, Paris, France

Abstract

Objectives: Liver metastasis from a neuroendocrine tumour (NET) represents a significant clinical entity. A multidisciplinary group of experts was convened to develop state-of-the-art recommendations for its management.

Methods: Peer-reviewed published reports on intra-arterial therapies for NET hepatic metastases were reviewed and the findings presented to a jury of peers. The therapies reviewed included transarterial embolization (TAE), transarterial chemoembolization (TACE) and radioembolization (RE). Two systems were used to evaluate the level of evidence in each publication: (i) the US National Cancer Institute (NCI) system, and (ii) the GRADE system.

Results: Eighteen publications were reviewed. These comprised 11 reports on TAE or TACE and seven on RE. Four questions posed to the panel were answered and recommendations offered.
Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference

Andrew Kennedy¹, Lourens Bester², Riad Salem³, Ricky A. Sharma⁴, Rowan W. Parks⁵ & Philippe Ruszniewski⁶

115 articles identified using the keywords:
neuroendocrine; liver;
hepatic; metastases;
chemoembolization; embolization;
TACE; TAE; radioembolization;
microspheres, and drug-eluting beads

Applying time period of 1995-2012

84 articles examined

Excluding non-English, single-case reviews, review articles, case reports, editorial, commentary articles, abstracts, posters

47 articles

Excluding heterogeneous patient cohorts, repeat publications, and studies with inadequate and insufficient data

18 articles included in final analysis

### SIRT evidence

**Table 2** Outcomes of studies of radioembolization in patients with liver metastases from neuroendocrine tumours

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Device used</th>
<th>Toxicity</th>
<th>Radiological response (RECIST 1.0)</th>
<th>Survival times and rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhee et al.</td>
<td>42</td>
<td>Yttrium-90 (glass)</td>
<td>Grade III/IV (14%)</td>
<td>54%</td>
<td>Median: 22 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yttrium-90 (resin)</td>
<td></td>
<td>50%</td>
<td>Median: 28 months</td>
</tr>
<tr>
<td>Kennedy et al.</td>
<td>148</td>
<td>Yttrium-90 (resin)</td>
<td>33% (grade III), fatigue (6.5%)</td>
<td>63%</td>
<td>Median: 70 months</td>
</tr>
<tr>
<td>King et al.</td>
<td>58</td>
<td>Yttrium-90 (resin) plus 5-FU</td>
<td>Radiation gastritis (2 patients), duodenal ulcer (1 patient)</td>
<td>39%</td>
<td>Median: 36 months 1-, 2- and 3-year survival: 86%, 58% and 47%, respectively</td>
</tr>
<tr>
<td>Saxena et al.</td>
<td>48</td>
<td>Yttrium-90 (resin)</td>
<td>0.5% (grade III) 1 patient (biliary obstruction)</td>
<td>54%</td>
<td>Median: 35 months 1-, 2- and 3-year survival: 87%, 62% and 42%, respectively</td>
</tr>
<tr>
<td>Cao et al.</td>
<td>58</td>
<td>Yttrium-90 (resin) plus 5-FU</td>
<td>Not reported</td>
<td>39.2%</td>
<td>Median: 36 months</td>
</tr>
<tr>
<td>Paprottka et al.</td>
<td>42</td>
<td>Yttrium-90 (resin)</td>
<td>0% grade III</td>
<td>22.5%</td>
<td>Median: 95% at 16.2 months</td>
</tr>
<tr>
<td>Memon et al.</td>
<td>40</td>
<td>Yttrium-90 (glass)</td>
<td>Fatigue (63%, all grades), nausea/vomiting (40%, all grades), grade III, IV (bilirubin, 8%; albumin, 2%; lymphocyte, 38%)</td>
<td>WHO: 64.0%; EASL: 71.4%</td>
<td>Median: 34.4 months 1-, 2- and 3-year survival: 72.5%, 62.5%, 45.0%, respectively</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; EASL, European Association for the Study of the Liver; WHO, World Health Organization.

**Total = 436 patients**  
**median 54% (22 – 71.4%)**


90Y microspheres in mNET: 
Retrospective analysis in 148 patients


**90Y microspheres in mNET:**

**Primary Tumor Site & Histology**

<table>
<thead>
<tr>
<th>Site of Primary Tumor</th>
<th>(n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Intestine</td>
<td>100</td>
</tr>
<tr>
<td>Pancreas</td>
<td>28</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>(n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid (NOS)</td>
<td>121</td>
</tr>
<tr>
<td>Islet Cell</td>
<td>15</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>3</td>
</tr>
<tr>
<td>Atypical</td>
<td>3</td>
</tr>
<tr>
<td>Glucogonoma</td>
<td>3</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>2</td>
</tr>
<tr>
<td>VIPoma</td>
<td>1</td>
</tr>
</tbody>
</table>

90Y microspheres in mNET: Radiographic Response

CT, MRI and OctreoScan imaging (n = 168 of 185 Tx)

- Complete response: 2.7%
- Partial response: 60.5% (73.2%)
- Stable disease: 22.7%
- Progressive disease: 4.9%
- Unknown response 9.1%

- Typical response noted by 12 weeks, some responses not stable until 9 months post-treatment

$^{90}$Y microspheres in mNET: Neuroendocrine Response

Pre-Treatment

3 Months Post-Treatment
$^{90}$Y microspheres in mNET: Carcinoid Response

Pre-Treatment

3–24 months pre-treatment
$^{90}$Y microspheres in mNET: Overall Survival

148 patients; 185 treatments

Median Survival: 70 months

95% CI

$^{90}$Y microspheres + 5FU in mNET: First prospective phase II study


90Y microspheres + 5FU in mNET: Radiographic Response

CT imaging by RECIST

- Complete response: 6 (18%)
- Partial response: 11 (32%)
- Stable disease: 5 (15%)
- Progressive disease: 11 (32%)
- Unknown response: 1 (3%)

Objective Response: 50%
Disease Control: 65%

$^{90}$Y microspheres + 5FU in mNET: Radiographic Response

CT imaging before and 27 months after SIRT in a patient who had a CR in the liver

CT imaging before and 36 months after SIRT in a patient who had a CR in the liver

$^{90}$Y microspheres in salvage therapy for treatment-refractory mNET: A prospective pilot study

**90Y microspheres in mNET salvage therapy: Radiographic Response**

CT imaging by RECIST

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
</tr>
<tr>
<td>Unknown response</td>
<td>0</td>
</tr>
</tbody>
</table>

Objective Response: 67%

Disease Control: 100%

Kalinowski *et al.* *Digestion* 2009; **79**: 137–42.
$^{90}\text{Y}$ microspheres in mNET salvage therapy: Biochemical Response

CgA (U/L)

Pre-SIRT SIRT 6 9 12

$^{90}$Y microspheres in mNET salvage therapy: Quality of Life

- Significant improvement in quality of life overall ($P < 0.05$)

$^{90}$Y microspheres in mNET salvage therapy: Overall Survival

- 9 patients; 12 treatments
- Mean follow-up: 21.7 mo ($\pm12.9$)
- Median Survival: not reached
- 1-year Survival: 100%
- 2-year Survival: 57%
- 3-year Survival: 57%

# Key TACE / TAE Studies

640 patients: TACE (466) vs Bland (174)  11.1% - 100%

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Tx Device</th>
<th>RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dong</td>
<td>123</td>
<td>TACE</td>
<td>62%</td>
</tr>
<tr>
<td>2. de Baere</td>
<td>20</td>
<td>TACE Doxorubicin beads</td>
<td>80%</td>
</tr>
<tr>
<td>3. Vogl</td>
<td>48</td>
<td>TACE (Mito C, Gemzar)</td>
<td>11.1% / 23.3%</td>
</tr>
<tr>
<td>4. Loewe</td>
<td>23</td>
<td>Bland</td>
<td>73%</td>
</tr>
<tr>
<td>5. Eriksson</td>
<td>41</td>
<td>Bland</td>
<td>50%</td>
</tr>
<tr>
<td>6. Pitt</td>
<td>100</td>
<td>TACE (49) vs Bland (51)</td>
<td>N/A</td>
</tr>
<tr>
<td>7. Ruutiainen</td>
<td>67</td>
<td>TACE (44) vs Bland (23)</td>
<td>22% vs 38%</td>
</tr>
<tr>
<td>8. Gupta</td>
<td>49</td>
<td>TACE (27) vs Bland (42)</td>
<td>50% vs 25%</td>
</tr>
<tr>
<td>9. Maire</td>
<td>26</td>
<td>TACE (12) vs. Bland (14)</td>
<td>100% vs 92%</td>
</tr>
<tr>
<td>10. Guiu</td>
<td>120</td>
<td>DEB-TACE mNET</td>
<td>N/A</td>
</tr>
<tr>
<td>11. Ruszniewski</td>
<td>23</td>
<td>TACE</td>
<td>61% PR, 22% SD, 17% PD TTP 14 mo.</td>
</tr>
</tbody>
</table>

## SIRT Key Studies\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Type</th>
<th>NCI [evidence &amp; endpoints]</th>
<th>GRADE [evidence]</th>
</tr>
</thead>
<tbody>
<tr>
<td>King</td>
<td>34</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
</tr>
<tr>
<td>Memon</td>
<td>40</td>
<td>Phase II</td>
<td>2-A</td>
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<tr>
<td>Rhee</td>
<td>42</td>
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<tr>
<td>Saxena</td>
<td>48</td>
<td>Phase II</td>
<td>2-A</td>
<td>B</td>
</tr>
<tr>
<td>Kennedy</td>
<td>148</td>
<td>Retrospective</td>
<td>3-ii-A</td>
<td>C</td>
</tr>
</tbody>
</table>

The GRADE system: 4 factors in strength of a recommendation: balance between desirable and undesirable effects, the quality of the evidence, values and preferences, and finally, costs.

\textsuperscript{1}National Cancer Institute: PDQ Levels of Evidence for Adult and Pediatric Cancer Treatment Studies. Bethesda, MD.

\textsuperscript{2}Guyatt. Going from evidence to recommendations. BMJ 2008; 336: 1049-1051.
Conclusion: ‘Radioembolization may have advantages over TAE and TACE because it causes fewer side-effects and requires fewer treatments. Based on current European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines, RE can be substituted for TAE or TACE in patients with either liver-only disease or those with limited extrahepatic metastases.’
The Efficacy of Hepatic $^{90}$Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis

Zlatko Devcic$^1$, Jarrett Rosenberg$^2$, Arthur J.A. Braat$^3$, Tust Techasith$^1$, Arjun Banerjee$^1$, Daniel Y. Sze$^1$, and Marnix G.E.H. Lam$^{1,3}$

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

“The pooled response rates compare favorably with other therapies such as somatostatin analogs with or without interferon; older cytotoxic chemotherapeutics [...] , systemic radionuclide therapies such as peptide receptor radionuclide therapy; and newer targeted systemic therapies including everolimus and sunitinib. Hepatic radioembolisation using $^{90}$Y resin microspheres is an effective treatment option for hepatic mNETs.”

Conclusions: SIRT for mNET

- SIRT with $^{90}$Y microspheres shows high response rates and disease control rates in the treatment of NET liver metastases.

- Moderate quality studies support the use of SIRT possibly instead of TAE, TACE in NET liver metastases.

- **SIRT** may have advantages over TAE/TACE in **reduced side effects** and fewer treatments in a significant percentage of patients.

- Based on current ENETs Consensus Guidelines, SIRT can be substituted for TAE/TACE in patients with liver-only disease and with limited extrahepatic metastases.