Radioisotopes in Medical Practice: From There to Here

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University of Alberta
Simplistic View of Medical Imaging

- X-rays - Images of Structure
- U/S - Images of Structure
- MRI - Images of Structure
- Isotopes - Images of Function
- Biomarkers/Images of Biology
Nuclear Medicine

Imaging

Single Photon

Planar

SPECT

Molecular Imaging

Imaging Biomarkers

Therapy

PET

Theranostics

\downarrow \text{ or } \alpha \text{ Particle}
Single Photon Imaging

- Radiopharmaceutical/Radiotracer
  - Radionuclide
    - Tc-99m
    - I-131
    - I-123
    - In-111
  - Probe
    - MDP - Bone
    - DTPA - Kidney/transit
    - MIBI - Cardiac perfusion
    - WBC - Infection
    - Peptide - Neuroendocrine cancers
A study of the histopathology and physiologic function of thyroid tumors, using radioactive iodine and radioautography
Dobyns BM and Lennon B.
*J Clin Endocrinol* 1948; 8:732-748

1. The degree of function may be related to the degree of cellular differentiation of adenomas, with certain exceptions.

2. There are hyperplastic adenomas with cellular hypertrophy which are hyperfunctioning but there are also hyperplastic adenomas which are not functioning.

3. Hyperfunctioning adenomas may exist with or without evidence of thyrotoxicosis and probably by their excessive activity suppress otherwise normal thyroid tissue.
Colloid adenoma with relatively little function
A - histologic section; B - radioautograph

Dobyns BM and Lennon B. *J Clin Endocrinol* 1948; 8:732-748
Thyroid Imaging 1976 – Iodine-131: Rectilinear Scanner
Treatment of Thyroid Cancer – 1953
No significant change in 2017

“Principal goal in the treatment of metastatic thyroid cancer is destruction of metastases with radioactive iodine”

- removal of all thyroid tissue
- suppression of iodide production by large doses of thiouracil
- stimulation by TSH

First Tc-99m Generator – Brookhaven National Laboratory

https://upload.wikimedia.org/wikipedia/commons/2/25/First_technetium-99m_generator_-_1958.jpg
The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."
Technetium -99m Generator 2015

Schematic diagram of new Tc-99m Generator @RIPD

Bone Scan 1974 $^{99m}$Tc PYP
Spinal Pleural Fistula Post Trauma 1989 $^{99m}$Tc DTPA
Brain Scan 1988 – $^{99m}\text{TcO}_4$
Splenunculi Post Trauma 1990 $^{99m}$Tc RBC
Metastatic Mediastinal Carcinoid: \(^{111}\text{In}\) Octreotide
Metastatic Mediastinal Carcinoid: $^{111}$In Octreotide SPECT
SPECT/CT I-131 Scan Thyroid Metastasis
Characteristics of PET/CT - Molecular Imaging; Imaging Biomarkers

• Assay of biological and functional tumor characteristics
  – Molecular medicine

• Targeted
  – To tumor
  – To biological process or target
  – To metabolic, biochemical, genomic, proteomic pathway

• Quantitative
  – Relative, absolute or temporal

• Diagnostic and predictive
  – Stratifies for treatment
  – Demonstrates early changes in response to therapy
  – Predicts treatment response
Characteristics of PET/CT - Molecular Imaging; Imaging Biomarkers

• Radiopharmaceutical/Radiotracer
  – Radionuclide
    • F-18
    • C-11
    • Ga-68
    • Rb-82
  – Probe
    • FDG - glucose metabolism
    • FAZA - hypoxia
    • FLT - proliferation
    • Peptide - neuroendocrine and prostate cancers
    • Carfentanil - opioid receptors
Coronal Slices of PET FDG Images
FDG PET Images Taken After Walking Without (A) or With (B) a Stride Assistance System

FDG Uptake by Lower Extremity Muscles During Walking With or Without a Stride Assistance System

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Without the SAS Mean</th>
<th>With the SAS Mean</th>
<th>Ratio with ÷ without</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor hallucis longus</td>
<td>2.08</td>
<td>2.36</td>
<td>1.25</td>
<td>0.43</td>
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<tr>
<td>Tibialis anterior</td>
<td>1.71</td>
<td>2.54</td>
<td>1.74</td>
<td>0.08</td>
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<tr>
<td>Tibialis posterior</td>
<td>1.44</td>
<td>2.92</td>
<td>2.13</td>
<td>0.04</td>
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<tr>
<td>Medial gastrocnemius</td>
<td>1.54</td>
<td>2.91</td>
<td>2.36</td>
<td>0.01</td>
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<tr>
<td>Rectus femoris</td>
<td>0.43</td>
<td>0.41</td>
<td>0.97</td>
<td>0.56</td>
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</tbody>
</table>

Molecular Profiling of Cancer – the Future of Cancer Medicine: a Primer on Cancer Biology and the Tools Necessary to Bring it to the Clinic

“The goal of personalized cancer medicine is to understand the relevant characteristics underlying a particular individual's disease (both disease and host factors) and then tailor therapy to that individual disease. The right drug, at the right dose, for the right patient at the right time is the goal of personalized medicine.”

Stricker T et al. Semin Oncol 38: 173 - 185
Assessment of Response
Tumors as Complex Tissues

The Reductionist View

A Heterotypic Cell Biology

---

Hanahan D and Weinberg RA. *Cell* 2000; 100:57-70
Tumors as Complex Tissues

Hanahan D and Weinberg RA. *Cell* 2011; 144:646 - 674
What is Measurable with Molecular Imaging
Workman P, et al. JNCI, 2006; 98(9):580-598

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Measurable Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>Expression of molecular target (erbB2), Physiologic state (hypoxia)</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Concentrations needed for activity at the site of action</td>
<td>Pharmacokinetic properties in plasma and/or tissue</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Specific action on the molecular target or pathway</td>
<td>Target inhibition in tumors and/or surrogate normal tissue</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Induction of the desired biologic effect</td>
<td>Inhibition of proliferation, invasion, angiogenesis, induction of apoptosis, differentiation or senescence</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Resulting clinical response</td>
<td>Tumor regression, cytostasis</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Patient outcome</td>
<td>Disease-free survival, performance status, quality of life, overall survival</td>
</tr>
</tbody>
</table>
Molecular Imaging/Imaging Biomarkers in Oncology

Current Paradigm

- Identify the presence or absence of tumor
  - Primary diagnosis and staging
  - Treatment effect
  - Monitoring
  - Recurrence
  - Follow-up and restaging
- Assessing toxicity
- Screening

Future Paradigm

- Current indications
- Biological characterization
  - Tumor
  - Individual
- Predicting progression/outcome
- Predicting/assaying Rx response
- Treatment stratification
- Predicting/assaying toxicity
- Personalized medicine
Imaging: Key to Better Health
FLT Uptake in Low- and High-Grade Sarcoma

# Mean and Maximal SUV and Tumor/NonTumor Ratio in Japanese Grading System

<table>
<thead>
<tr>
<th></th>
<th>Grade 1 (n=7)</th>
<th>Grade 2 (n=5)</th>
<th>Grade 3 (n=8)</th>
<th>Low vs High</th>
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<tbody>
<tr>
<td>Mean SUV</td>
<td>1.0</td>
<td>2.1</td>
<td>2.8</td>
<td>0.011</td>
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<tr>
<td>Maximal SUV</td>
<td>1.3</td>
<td>2.8</td>
<td>3.3</td>
<td>0.014</td>
</tr>
<tr>
<td>TNT</td>
<td>2.1</td>
<td>3.4</td>
<td>6.0</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Imaging with FLT in 2 Patients with NSCLC

Normal Distribution

Abnormal Distribution
Metabolic Assessment of Gliomas using $^{11}$C-Methionine, $[^{18}$F]$-$Fluorodeoxyglucose, and $^{11}$C-Choline Positron-Emission Tomography
Metabolic Assessment of Gliomas

- 95 patients with presentation with glioma
  - Brain stem and grade 1 excluded
- Presurgical evaluation with MET, FDG, CHO, contrast enhanced MRI
- Correlation with WHO histological classification

**Fig 2.** Left top, Contrast-enhanced, T1-weighted image. Right top, MET PET is superimposed on MR imaging. Left bottom, CHO PET is superimposed on MR imaging. Right bottom, FDG PET is superimposed on MR imaging.

A; A 32-year-old woman presented with diffuse astrocytoma. MET T/N ratio = 1.72, CHO T/N ratio = 1.38, and FDG T/N ratio = 0.86. B; A 25-year-old woman presented with oligoastrocytoma. MET T/N ratio = 2.76, CHO T/N ratio = 1.92, and FDG T/N ratio = 0.92. C; A 44-year-old man presented with oligodendroglioma. MET T/N ratio = 3.71, CHO T/N ratio = 2.74, and FDG T/N ratio = 1.07. D; A 62-year-old woman presented with anaplastic astrocytoma. MET T/N ratio = 4.26, CHO T/N ratio = 10.17, and FDG T/N ratio = 1.24. E; A 68-year-old man presented with glioblastoma multiforme. MET T/N ratio = 6.85, CHO T/N ratio = 33.38, and FDG T/N ratio = 2.55.
Correlation Between Tracer Uptake and Tumour Grade
$^{11}$C-Carfentanil Distribution in Brain
Hypoxia Imaging in GBM - FAZA
Hypoxia Imaging: Tirapazamine Trial

FDG Pre Rx
FDG Post Rx

FMISO Pre Rx

KM Survival Standard of Care
– v – SOC + Tirapazamine
Functional imaging of neuroendocrine tumors with combined PET/CT with $^{68}$Ga-DOTATATE and $^{18}$F-FDG


• 38 patients with prior diagnosis of NETs
  – 34 GEP
  – 4 Unknown primary
• Gold standard: Histology, markers, Progressive imaging
• Ga-68 sensitivity: 82%
• FDG sensitivity: 66%
Imaging Biomarkers for Cancer Biology

Figure: Hanahan D and Weinberg R, 2011, Cell, 144:646-674, adapted by Aboagye E, Maxwell R and Newell DR
Criteria for Assessing the Prognosis of Neuroendocrine Tumors of the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Biologial behaviour</th>
<th>Metastases index</th>
<th>Histological Invasion</th>
<th>Tumor differentiation</th>
<th>Angio- stases size invasion</th>
<th>Ki-67</th>
<th>Hormonal</th>
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<tbody>
<tr>
<td>Benign</td>
<td>-</td>
<td>Well</td>
<td>≤ 1 cm</td>
<td>-</td>
<td>&lt; 2%</td>
<td>-</td>
</tr>
<tr>
<td>Benign or low grade</td>
<td>-</td>
<td>Well</td>
<td>≤ 2 cm</td>
<td>-/+</td>
<td>&lt; 2%</td>
<td>-</td>
</tr>
<tr>
<td>Low grade malignant</td>
<td>+</td>
<td>+</td>
<td>Well</td>
<td>&gt; 2 m</td>
<td>+</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>High grade malignant</td>
<td>+</td>
<td>+</td>
<td>Poorly</td>
<td>Any</td>
<td>+</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>

54-year-old Female Patient with Metastatic Carcinoid Tumor (Primary Cecal Carcinoma)

55-yr-old Female Patient with Metastatic Neuroendocrine Carcinoma with Unknown Primary

## SUVmax of $^{68}$Ga-DOTATATE and $^{18}$F-FDG According to Tumor Grade

<table>
<thead>
<tr>
<th></th>
<th>$^{68}$Ga-DOTATATE</th>
<th>$^{18}$F-FDG</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NET</td>
<td>16.9 (1.6-50)</td>
<td>4.2 (1.4-16.4)</td>
<td>.005</td>
</tr>
<tr>
<td>Ki67 index &lt;2%</td>
<td>29 (3.3-45)</td>
<td>2.9 (1.5-12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ki67 index 3%-20%</td>
<td>15.5 (1.8-50)</td>
<td>10.5 (2.0-13.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Ki67 index &gt;20%</td>
<td>4.4 (1.6-8.9)</td>
<td>11.7 (4.1-16.4)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Radioisotope Therapy (RIT)
Lu-177 DOTATATE Treatment for Patients with Neuroendocrine Tumours

Sandy McEwan, M.B. F.R.C.P.C
Chair, Department of Oncology
University of Alberta
Treatment With the Radiolabeled Somatostatin Analog $[^{177}\text{Lu}-\text{DOTA}^0,\text{Tyr}^3]\text{Octreotate}$: Toxicity, Efficacy, and Survival

Dik J. Kwekkeboom, et al

*JCO*, 2008:2124-2130
Lutetium Octreotate Rx Survival in GEPNETS


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## Previous PRRT monotherapy studies in NET

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Patients</th>
<th>Compound</th>
<th>Primary Tumor</th>
<th>Mean Dose (GBq)</th>
<th>Mean Cycles (N)</th>
<th>DCR (%)</th>
<th>PFS (M)</th>
<th>OS (M)</th>
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<tbody>
<tr>
<td><strong>MEDICAL THERAPIES</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Yao 2011 (19)</td>
<td>P</td>
<td>207</td>
<td>Everolimus</td>
<td>P-NET</td>
<td>10mg daily</td>
<td>78</td>
<td>11</td>
<td>&gt;28</td>
<td></td>
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<tr>
<td>Raymond (20)</td>
<td>P</td>
<td>86</td>
<td>Sunitinib</td>
<td>P-NET</td>
<td>37.5 mg daily</td>
<td>72</td>
<td>11.4</td>
<td>&gt;20</td>
<td></td>
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<tr>
<td>Rinke (22)</td>
<td>P</td>
<td>42</td>
<td>Octreotide</td>
<td>GE-NET</td>
<td>30 µg 4-weekly</td>
<td>NA</td>
<td>14.3</td>
<td>&gt;75</td>
<td></td>
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<tr>
<td>Martin-Richard 2013 (21)</td>
<td>R</td>
<td>30</td>
<td>Lanreotide</td>
<td>ALL NET</td>
<td>120 mg 4-weekly</td>
<td>89</td>
<td>12.9</td>
<td>NA</td>
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<tr>
<td><strong>PRRT</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Waldherr 2001 (2)</td>
<td>P</td>
<td>41</td>
<td>$^{90}$Y-TOC</td>
<td>ALL NET</td>
<td>6/m² 4-weekly</td>
<td>85</td>
<td>&gt;26</td>
<td>&gt;24</td>
<td></td>
</tr>
<tr>
<td>Imhof 2011 (3)</td>
<td>R</td>
<td>1109</td>
<td>$^{90}$Y-TOC</td>
<td>ALL NET</td>
<td>3.7/m² *Cycle (1-10)</td>
<td>85</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>Kwekkeboom 2008 (4)</td>
<td>R</td>
<td>310</td>
<td>$^{177}$LU-TATE</td>
<td>ALL NET</td>
<td>28.7 4-weekly</td>
<td>80.3</td>
<td>33</td>
<td>46</td>
<td></td>
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<tr>
<td>Bodei 2011 (9)</td>
<td>P</td>
<td>51</td>
<td>$^{177}$LU-TATE</td>
<td>ALL NET</td>
<td>25.2-26.4 4-weekly</td>
<td>82</td>
<td>36</td>
<td>36&gt;</td>
<td></td>
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<tr>
<td>Sansovini 2013 (10)</td>
<td>P</td>
<td>52</td>
<td>$^{177}$LU-TATE</td>
<td>P-NET (all)</td>
<td>81 2-weekly</td>
<td>81</td>
<td>29</td>
<td>&gt;30</td>
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<tr>
<td>Ezziddin 2014 (8)</td>
<td>R</td>
<td>68</td>
<td>$^{177}$LU-TATE</td>
<td>P-NET</td>
<td>32 4-weekly</td>
<td>85</td>
<td>34</td>
<td>53</td>
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<tr>
<td>Paganeli 2014 (11)</td>
<td>P</td>
<td>43</td>
<td>$^{177}$LU-TATE</td>
<td>GE-NET</td>
<td>18.4-25.7 5-weekly</td>
<td>84</td>
<td>36</td>
<td>&gt;60</td>
<td></td>
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<tr>
<td>Romer 2014 (6)</td>
<td>R</td>
<td>141</td>
<td>$^{177}$LU-TOC</td>
<td>ALL NET</td>
<td>13.5 2-weekly</td>
<td>NA</td>
<td>NA</td>
<td>45.5</td>
<td></td>
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<tr>
<td>Present Study</td>
<td>R</td>
<td>56</td>
<td>$^{177}$LU-TOC</td>
<td>ALL NET</td>
<td>13.1 2-weekly</td>
<td>66.1</td>
<td>17.4</td>
<td>34.2</td>
<td></td>
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<td></td>
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<td>29.2</td>
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<td>100</td>
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<td>34.7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75</td>
<td>11.9</td>
<td>16.2</td>
<td></td>
</tr>
</tbody>
</table>

*BL SD - Percept Patients with Stable Disease at Baseline*
Radioisotope Therapy (RIT)

The systemic administration of a targeted radionuclide utilizing short range beta (alpha) particle or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer:

- Symptom control; improved quality of life
- Stable disease
- (Good) partial remission
- Complete remission
- Prolonged response times
  - Increased progression free survival
  - Increased overall survival
Treatment Delivery in RIT

• Current paradigm continues to be governed by:
  – Classical radiobiology
  – Classical dosimetry
  – Fixation on tumor dose

• Emulation of classical external beam radiation oncology principles

• “First dose is best (only) chance of clinical benefit”

• Lack of appropriate clinical trial methodology

• Lack of robust clinical outcomes data
Two Paradigms for RIT

- **“Big Bang”**
  - High unit dose
  - Toxicity rescue
  - Single treatment
  - Possibly precludes further treatments
  - High complexity
  - Always inpatient

- **“Steady State”**
  - Low unit dose
  - High cumulative dose
  - Multiple treatments
  - Titrate to toxicity
  - Delayed Response
  - Low complexity
  - Usually outpatient

Paradigm of Physics  Paradigm of Biology
The Edmonton Protocol
The Edmonton Lu-177 Protocol

**Hypothesis:** Induction & long-term maintenance therapy with Lu-177 improves outcomes in patients with NETs, and is effective and safe for these patients.

**Clinical Protocol:** up to 12 cycles in total

*Induction:* 4 cycles of up to 6.11 GBq/cycle every 2.5 – 3.5 months

*Maintenance:* up to 8 cycles of up to 4.07 GBq/cycle every 5.5 – 10 months
## Edmonton Protocol

<table>
<thead>
<tr>
<th>Therapy Number</th>
<th>Year</th>
<th>Frequency</th>
<th>Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>1</td>
<td>Every 10 - 12 weeks</td>
<td>CT/MRI scans and blood work/urine 4 months after therapy 4.</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>1 - 4</td>
<td>Every 10 - 12 weeks</td>
<td>CT/MRI scans and blood work/urine 4 months after therapy 4.</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>2</td>
<td>Every 6 months (range 5 – 8 months)</td>
<td>CT/MRI scans and blood work/urine 4 months after therapy 5 &amp; 6.</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>5 - 6</td>
<td>Every 6 months (range 5 – 9 months)</td>
<td>CT/MRI scans and blood work/urine 4 months after therapy 7 &amp; 8.</td>
</tr>
<tr>
<td><strong>7 - 8</strong></td>
<td>3</td>
<td>Every 6 months (range 5 – 9 months)</td>
<td>CT/MRI scans and blood work/urine 4 months after therapy 7 &amp; 8.</td>
</tr>
<tr>
<td><strong>9 +</strong></td>
<td>4</td>
<td>Every 9 months (range 7 – 12 months)</td>
<td>CT/MRI scans and blood work/urine 4 months after each subsequent therapy.</td>
</tr>
</tbody>
</table>
## Distribution of Lu-177 patients at CCI - GEPNETS

<table>
<thead>
<tr>
<th>Subjects with at least 1 treatment</th>
<th>n = 138</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>PNET n=44; GNET n=84, presumptive GNET n=10</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs) at treatment onset (mean, range)</strong></td>
<td>61.3 (26.5 – 84.4)</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>74/64</td>
</tr>
</tbody>
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### Current Active Patients: March 31, 2016

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Therapy</td>
<td>109</td>
</tr>
<tr>
<td>No Longer on therapy</td>
<td>29</td>
</tr>
<tr>
<td>Deceased</td>
<td>13</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>9</td>
</tr>
<tr>
<td>On Hold - Toxicity</td>
<td>5</td>
</tr>
<tr>
<td>Complete Remission</td>
<td>2</td>
</tr>
</tbody>
</table>
## Cumulative Administered Lu-177 Doses

<table>
<thead>
<tr>
<th>Total # Lu-177 Doses</th>
<th>Cumulative Lu dose (GBq) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 2</td>
<td>5.76 (2.4)</td>
</tr>
<tr>
<td>3 - 4</td>
<td>17.90 (3.4)</td>
</tr>
<tr>
<td>5 - 6</td>
<td>23.49 (3.9)</td>
</tr>
<tr>
<td>7 - 8</td>
<td>31.98 (4.3)</td>
</tr>
<tr>
<td>9 - 10</td>
<td>40.25 (2.9)</td>
</tr>
<tr>
<td>11 - 12</td>
<td>48.88 (6.0)</td>
</tr>
</tbody>
</table>
# Rx Failures by Primary Site

<table>
<thead>
<tr>
<th>Site</th>
<th>No Longer on Rx</th>
<th>Deceased</th>
<th>PD</th>
<th>CR</th>
<th>On Hold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNET</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GNET</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>pGNET</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Progression Free Survival

Median PFS > 54 months
Surgical CR After 6 Cycles

NM “CR” After 6 Cycles
PET “CR”
After 6 Cycles

Jan 2013

Jan 2015
Lu-177 Therapy Overview All Diagnoses

- Data support hypothesis that induction and maintenance therapy with Lu-177 improves PFS in patients with GEPNETS.
- This regimen is more effective than literature reported treatment regimens.
- In this cohort, median PFS has not been reached at 54 months.
- GNET response rate > PNET
  - 80% -v- 62%
Edmonton Protocol Toxicity

- Lymphocytes ≥ grade 3: n = 10
- Platelets ≥ grade 3: n = 1
- White cells ≥ grade 3: n = 1
- Renal ≥ grade 3: n = 4
- No myelodysplasia or leukemia has been observed
Clinical Outcomes after Steady State RIT (Biological Hypothesis; Edmonton Protocol)

- Stable disease is common
- Palliative responses are the norm
  - There appears to be a cumulative dose benefit
  - Treatments may be sustained for several years
  - There appears to be limited cumulative dose risk
  - Treatments may continue as maintenance
  - Response may be sustained for several years
- Unequivocal progression free survival benefit
- Probable overall survival benefit
- Toxicity is very limited; is acceptable at the doses administered and should not reduce therapy goals of improving long term responses
- Implications for combination therapies
How Does it Work

(Biological Hypothesis)
# Characteristics of Radioisotope Therapy

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Scientific Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systemic administration</td>
<td>• VLDR/LDR</td>
</tr>
<tr>
<td>• Retreatment</td>
<td>• <em>Microdosimetry (biology)</em></td>
</tr>
<tr>
<td>• Low toxicity</td>
<td>• $T_p$ correlates with $T_b$</td>
</tr>
<tr>
<td>• Low complexity</td>
<td>• Low proliferation rate (?)</td>
</tr>
<tr>
<td>• Adjuvant treatment (?)</td>
<td>• Ability to image (theragnostic)</td>
</tr>
<tr>
<td></td>
<td>• Specific targeting</td>
</tr>
</tbody>
</table>
“Classical” Cell Survival Curves

- Cell killing is well described by shouldered models such as multi-target [MT] or linear-quadratic [LQ].

- Cells must be “hit” to be killed, and DNA is the principal “target”.
Paradigm Revision:
Low dose hypersensitivity-inducible radioresistance (LDH-IRR)

• Most cell types exhibit fine structure in their survival curves at low doses.

Survival curves for HT-29 cells

Ref: Wouters B et al.
Survival Curves - LDHRS

Clinical relevance for LDH in RIT

- If localized dose/dose rate is below the threshold for triggering IRR, cell killing should follow the initial slope of the survival ($\alpha_s$) rather than $\alpha_r$ estimated from high-dose LQ model.
- If so RIT should exert much greater cytotoxicity than would be predicted by conventional LQ models.
- Is RIT effectively “ultra fractionation” which fails to activate IRR.
LDR Evades DNA Repair Sensors

- Reduced activation of ATM following LDR
- Reduced activation of downstream target gH2AX
- Increased cell killing after LDR

“Failure to activate ATM-associated repair pathways contributes to the increased lethality of continuous LDR radiation exposures”

Lack of DSB Repair After Very Low Doses

- Rothkamm and Löbrich (2003) observed a decreasing capacity for DSB repair with decreasing dose.
- Between 2 Gy and 5 mGy, H2AX foci were extensively repaired.
- Below 1.2 mGy, repair of foci did not occur up to 24 h.
p53 also transcriptionally transactivates genes such as \( p21^{\text{waf1/cip1}} \).

Different types of normal cells lose their clonogenic potential by several different mechanisms (necrosis, apoptosis, replicative senescence).

Many human tumor cells have mutant p53 and fail to properly execute these responses ... can this be exploited therapeutically?
DNA Damage - Cellular Responses

Ionizing Radiation → Double-strand Break → Sensors, Transducers and Effectors

DNA repair

G1, S, G2, M

Accelerated Senescence

Apoptosis

To Cure Sometimes
To Help Often
To Care Always