Current Status of SRT

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Illustration of internal radionuclide therapy

Starting with a radionuclide that decays via alpha or beta decay

The radionuclide may be conjugated to a targeting agent (e.g. small molecule, antibody)

The targeted radionuclide therapy is administered to a patient

With time, the agent has higher accumulation in the target (e.g. tumor)

Unlike conventional radiation therapy, the targeting of the radiation therapy is biologic
What is internal radionuclide therapy?

Locally delivered radiation therapy, achieved through biologic targeting....

In addition, sometimes it is called ...

- Systemic Radionuclide Therapy
- Radionuclide Therapy
- Radiopharmaceutical Therapy
- Targeted Radionuclide Therapy
- Molecular Radiation Therapy

and may include...

- Selective Internal Radionuclide Therapy
- Peptide Receptor Radionuclide Therapy
- Radioimmunotherapy...
What radionuclides can be used?

- Local energy deposition (alpha, low energy betas)
- Half-life on the order of days (~5-15 days)
- Imaging analogue (e.g. $^{64}$Cu & $^{67}$Cu)
- Reliable production, simple radiochemistry
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>E or E(max) (MeV)</th>
<th>Photon Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>32P</strong></td>
<td>14.3 d</td>
<td>β-</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td><strong>64Cu</strong></td>
<td>12.7 h</td>
<td>β-, EC + β+</td>
<td>0.58; *: 0.65</td>
<td>None</td>
</tr>
<tr>
<td><strong>67Cu</strong></td>
<td>2.58 d</td>
<td>β-</td>
<td></td>
<td>91(7%), 93(16%), 185(49%)</td>
</tr>
<tr>
<td><strong>67Ga</strong></td>
<td>3.26 d</td>
<td>EC</td>
<td></td>
<td>91(3%), 93(39%), 185(21%), 300(17%), 394(5%)</td>
</tr>
<tr>
<td><strong>68Ga</strong></td>
<td>67.6 min</td>
<td>β+</td>
<td>1.9</td>
<td>1077</td>
</tr>
<tr>
<td><strong>89Sr</strong></td>
<td>50.5 d</td>
<td>β-</td>
<td>1.49</td>
<td>None</td>
</tr>
<tr>
<td><strong>90Y</strong></td>
<td>2.67 d</td>
<td>β-</td>
<td>2.28</td>
<td>None</td>
</tr>
<tr>
<td><strong>111In</strong></td>
<td>2.8 d</td>
<td>EC</td>
<td></td>
<td>171(90%), 245(94%)</td>
</tr>
<tr>
<td><strong>117mSn</strong></td>
<td>13.6 d</td>
<td>IT</td>
<td></td>
<td>159(86%)</td>
</tr>
<tr>
<td><strong>124I</strong></td>
<td>4.18 d</td>
<td>EC, b+</td>
<td></td>
<td>603 (60%), 723 (10%), 1325 (1.4%), 1376 (1.7%), 1509 (3%), 1691 (10.4%)</td>
</tr>
<tr>
<td><strong>131I</strong></td>
<td>8.02 d</td>
<td>β-</td>
<td>0.61</td>
<td>80(2.6%), 284(6%), 364(82%), 637(7%), 723(1.8%)</td>
</tr>
<tr>
<td><strong>153Sm</strong></td>
<td>1.95 d</td>
<td>β-</td>
<td>0.81</td>
<td>103(30%)</td>
</tr>
<tr>
<td><strong>166Ho</strong></td>
<td>26.8 h</td>
<td>β-</td>
<td>1.85</td>
<td>81(7%), 1379(0.93%), 1582(0.19%), 1662(0.12%)</td>
</tr>
<tr>
<td><strong>177Lu</strong></td>
<td>6.71 d</td>
<td>β-</td>
<td>0.5</td>
<td>113(6), 208(11%)</td>
</tr>
<tr>
<td><strong>186Re</strong></td>
<td>3.72 d</td>
<td>EC</td>
<td>1.07</td>
<td>137(9%)</td>
</tr>
<tr>
<td><strong>188Re</strong></td>
<td>17.0 h</td>
<td>β-</td>
<td>2.12</td>
<td>155(15%), 478(1%), 633(1%)</td>
</tr>
<tr>
<td><strong>211At</strong></td>
<td>7.2 h</td>
<td>EC, α</td>
<td>7.45</td>
<td>X rays 77(12%), 80(20%)</td>
</tr>
<tr>
<td><strong>213Bi</strong></td>
<td>45.6 min</td>
<td>B-, α</td>
<td>8</td>
<td>440(16.5%)</td>
</tr>
<tr>
<td><strong>223Ra</strong></td>
<td>11.4 d</td>
<td>β-, α</td>
<td>7.53</td>
<td>82(20%), 154(15%), 270(10%), 351, 405</td>
</tr>
<tr>
<td><strong>225Ac</strong></td>
<td>10.0 d</td>
<td>α</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Department of Energy continues to develop isotopes for use in medical applications.
Targeting Agents

• Potential of employing advances in pharmacologic targeting, for radiation therapy.

• If an alpha or beta emitting radionuclide can be conjugated with a targeted agent, this results in targeted radionuclide therapy.

• The level of targeting varies from simplistic (e.g. $^{131}$I, $^{223}$Ra-dichloride), to very complicated (e.g. conjugating radionuclides to peptides and antibodies)
Targeting Agents

Example (1)

Peptide Receptor Targeting

\(^{177}\text{Lu-Dotatate}\)
Targeting Agents

Example (2)

Prostate Specific Membrane Antigen

\(^{177}\text{Lu}-\text{PSMA-617}\)

FIGURE 1. PSMA equals enzyme glutamate carboxypeptidase II. Its proteolytic domain can be targeted with Glu-urea motif (green). Hydrophobic pocket accessory to proteolytic domain adversely interacts with highly polar chelates such as DOTA (red) but favors more lipophilic chelates (orange) such as CIM (MIP-1427) for labeling with \(^{90}\text{Y}\) or HBED-CC (PSMA-11) for labeling with \(^{68}\text{Tc}\). In PSMA-617, aromatic linker (yellow) exploits lipophilic accessory pocket to keep more universal DOTA-chelate remote to Glu-urea binding site.

PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with \(^{177}\text{Lu}\)-Labeled PSMA-617

Clemens Kratochwil\(^1\), Frederik L. Giesel\(^1,2\), Melsa Stefanova\(^1\), Martina Benešová\(^1\), Marcus Bronzel\(^2\), Ali Afshar-Oromieh\(^1,2\), Walter Mier\(^1\), Matthias Eder\(^1\), Klaus Kopka\(^3\), and Uwe Haberkorn\(^1,2\)
Targeting Agents

Example (3)

Antibody targeting

($^{90}$Y Ibritumomab tiuxetan)
Targeting: What can we treat?

Radionuclide therapy can be targeted in the same manner as other pharmaceuticals.
Targeted radionuclide therapy isn’t new

$^{131}$I is routinely used in the treatment of papillary and follicular thyroid cancer

(30-100 mCi dose)

Part of routine clinical practice

(Nuclear Medicine)
Targeted radionuclide therapy isn’t new (cont’d)

• Y-90 microspheres are used for the treatment of liver cancers.

• Administered activity is based on the liver mass and the required dose (e.g. 80-150 Gy for TheraSpheres)

\[
\text{Activity(GBq)} = \frac{\text{Dose(Gy)} \times \text{LiverMass(Kg)}}{50}
\]

• Part of routine clinical practice; may be a part of interventional radiology, nuclear medicine or radiation oncology

FDA approvals of targeted radionuclide therapy

- **1971** 
  - $^{131}$I- Sodium Iodide
  - $^{89}$Sr - Chloride

- **1993** 
  - Metastron

- **1999** 
  - $^{90}$Y - Microspheres
  - Theraspheres

- **2002** 
  - $^{90}$Y - Ibritumomab Tiuxetan
  - Zevalin

- **2002** 
  - $^{89}$Sr - Chloride
  - Metastron

- **2003-2014** 
  - $^{131}$I Tositumomab
  - Bexxar

- **2013** 
  - $^{223}$Ra-Dichloride
  - Xofigo

- **2018** 
  - $^{177}$Lu - Dotatate
  - Lutathera

- **2017** 
  - Post treatment Dosimetry Software for $^{90}$Y
  - MIM SurePlan

* Humanitarian Device Exemption (HDE)
** Premarket Approval (PMA)
FDA approvals of targeted radionuclide therapy

There are many agents that are currently in clinical trials

- Zevalin (Ibritumomab Tiuxetan) 2002
- Xofigo (223Ra-Dichloride) 2013
- Lutathera (177Lu-Dotatate) 2018

- Lutathera (177Lu-Dotatate) 2018
Clinical Trials: SRT in Development

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Conjugate Labeled</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutetium-177</td>
<td>PSMA</td>
<td>Metastatic Castration Resistant Prostate Cancer</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>Girentuximab</td>
<td>Metastatic Clear Cell Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>dis-HSG-DOTA peptide IMP-288</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>Lilotomab (Betalutin®)</td>
<td>Radioimmunotherapy for Treatment of Relapsed Non-Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>DOTA- cG250</td>
<td>Metastatic Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Indium-111</td>
<td>DOTA-cG250</td>
<td>Metastatic Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>CLR1401</td>
<td>Glioma</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>monoclonal antibody BC8</td>
<td>Non-Hodgkin Lymphoma</td>
</tr>
</tbody>
</table>
Clinical Trials: SRT in Development

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Conjugate Labeled</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium-225</td>
<td>Lintuzumab</td>
<td>Acute Myeloid Leukemia, Multiple Myeloma</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>DOTATOC</td>
<td>Neuroendocrine Tumor</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>In combination with immune modulation therapy</td>
<td>Hepatocellular Ca</td>
</tr>
<tr>
<td>Holmium-166</td>
<td>DOTMP</td>
<td>Ewing’s sarcoma</td>
</tr>
<tr>
<td>Lead-212</td>
<td>Trastuzumab</td>
<td>Multiple neoplasms</td>
</tr>
<tr>
<td>Lead-212</td>
<td>AlphaMedix®</td>
<td>Neuroendocrine Tumor</td>
</tr>
<tr>
<td>Bismuth-213</td>
<td>monoclonal M195</td>
<td>Leukemia, Myelodysplastic syndromes</td>
</tr>
</tbody>
</table>
Clinical Trials: SRT alone or in combination for multiple indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>In combination with:</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xofigo (Ra 223 dichloride)</td>
<td>Abiraterone</td>
<td>mCRPC</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stereotactic body radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Neoplasms, bone diseases</td>
</tr>
<tr>
<td></td>
<td>Hormonal Tx and Denosumab</td>
<td>Breast cancer with bone mets</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Approved indication: mCRPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutathera (Lu 177 dotatate)</td>
<td>Nivolumab</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Approved indication: GEP-NETs</td>
<td>N/A</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
Outcomes of SRT clinical trials

- For the mentioned clinical trials, the endpoints vary.

- The outcomes of the clinical trials may be:
  - Maximum tolerated dose
  - Progression free survival
  - Overall survival
  - Quality of life metrics

- Dosimetry for tumor volumes and organs at risk may not be included in the studies
Targets and Organs at Risk

In External Beam RT, we follow ICRU guidelines

• Include how we define where the radiation is prescribed (targets)
• Include how we report the radiation dose received by normal tissues (organs at risk)

• It should be noted that a target can be encompassed by an organ at risk.
Targets and Organs at Risk

In External Beam RT, ICRU guidelines are followed

**Treatment planning volumes**

1. **GTV**: Gross tumor volume
2. **CTV**: Clinical target volume
3. **PTV**: Planning target volume
What we do with the Organs at Risk Data

There are guidelines for maximum dose tolerances for high dose per fraction treatments (e.g. SBRT).

There are guidelines for what is used in conventional fractionation schemes as well.

In addition, there are guidelines on how to contour organs at risk (e.g. bowel)
What data do we have on radiation dose response?

In external beam radiation therapy, 7% is often quoted as the accuracy needed for modern radiation dosimetry.

There are also ways to externally verify our dosimetry (e.g. IROC phantoms)
What data do we have on radiation dose response?

Very little data is available on dose response in patients receiving radionuclide therapy.

In radionuclide therapy, the one variable controlled is the administered activity.

This may be determined based on a calculation of the patient’s body surface area.

Do not typically get dose to targets or OARs, and doses are rarely reported in Gy.
<table>
<thead>
<tr>
<th>Input</th>
<th>Dose Calculation</th>
<th>Optimization Parameters</th>
<th>Radiation Biology</th>
<th>End-Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Time-integrated activity in reference organs</td>
<td>Reference phantom based MIRD calculation</td>
<td>Risk models that relate equivalent or effective organ dose to risk: BEIR VII, ICRP, NCRP, EPA</td>
<td>Cancer risk and other health risks</td>
</tr>
<tr>
<td>RPT</td>
<td>Longitudinal activity, density and composition images</td>
<td>Monte Carlo/analytical methods, MIRD voxel S-Values.</td>
<td>Administered activity</td>
<td></td>
</tr>
<tr>
<td>External Beam RT</td>
<td>Patient Anatomy; Complete CT and contoured structures</td>
<td>Monte Carlo/analytical dose calculation algorithms.</td>
<td>Beam parameters (number of beams, weight, fluence, energy, etc.) optimized to meet dose volume histogram constraints.</td>
<td>Organ toxicity; tumor response</td>
</tr>
</tbody>
</table>
**Supplementary Table S2. \(^{177}\)Lu-DOTATATE Exposure.**

<table>
<thead>
<tr>
<th>No. of administrations</th>
<th>Patients who completed treatment phase (N=1031)</th>
<th>no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>79 (77)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12 (12)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>All treated patients (N=111)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No DMT</td>
<td>103 (93)</td>
<td></td>
</tr>
<tr>
<td>DMT</td>
<td>8 (7)</td>
<td></td>
</tr>
</tbody>
</table>

* DMT denotes dose-modifying toxicity.

† Excluding patients still under treatment (n=8) or no treatment (n = 5).
What do we learn (or change) when accurate dosimetry is performed?
What do we learn (or change) when accurate dosimetry is performed?

68Ga-DOTATOC (evaluate receptor targeting before therapy)

90Y-DOTATOC
Cycle 1

90Y-DOTATOC
Cycle 2

90Y-DOTATOC
Cycle 3

After each treatment, the uptake of 90Y-DOTATOC was imaged using PET/CT and SPECT/CT (renal imaging).

Doses for subsequent cycles were adjusted using renal dose estimates from previous cycles, maintaining total renal dose < 23 Gy.
What do we learn (or change) when accurate dosimetry is performed?

10/21 Patients had Cycle 2 Dose Increased > 20% as a result of 90Y-DOTATOC PET/CT Measurement

4/21 Patients had Cycle 2 Dose Decreased by >10% as a result of 90Y-DOTATOC PET/CT Measurement

3/21 Patients had Cycle 3 Dose Decreased by > 30% to keep Total Cumulative Kidney Dose < 23 Gray

Dose escalation prohibited by protocol in 2 pediatric cases

9/21 Patients likely would have benefited from even higher administered therapeutic doses, but were limited by protocol maximum injected dose of 5.6 GBq (150 mCi) [90Y]DOTATOC

Slide courtesy of M. Madsen
What data do we have on dose response?

A. Platelet toxicity as a function of administered activity
B. Platelet toxicity as a function of administered activity normalized to body surface area
C. Platelet toxicity as a function of marrow dose
D. Platelet toxicity as a function of whole body radiation dose
Targeted radionuclide therapy has a promising future

• The radiation is targeted and may spare healthy tissues

• Less dependent on user skill

• Targeting developments can follow pharmaceutical targeting developments

• May be cost effective .... (TBD)
Outlook

For the success of radionuclide therapy we need:

① Available radionuclides
② Ability to target the radiation
③ Accurate dosimetry for targets and organs at risk
④ Workflows (and dosimetry tools) that can be integrated into clinical environments
For accurate dosimetry, we need quantitative imaging

- For accurate dosimetry we need volumetric images of our patients (CT, MRI) to accurately determine target structures and organs at risk

- We also need functional imaging studies to determine the activity of the radiotracer in the volumes of interest

- Additional challenges include quantification of nuclear medicine studies, spatial resolution and kinetic modeling