Theranostic clinical trials outlook and the role of medical physics

Jacek Capala
Radiation Research Program
Division of Cancer Treatment and Diagnosis
NCI/NIH/HHS
Outline

• FDA-approved therapeutic radiopharmaceuticals
• Radiation dosimetry as a biomarker
• Treatment planning process and software
• Recent initiatives at professional societies (AAPM, SNMMI)
• Conclusions
## RPTs Approved before 2022

<table>
<thead>
<tr>
<th>RPT agent</th>
<th>Company</th>
<th>Indication</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium-223 chloride(^a)</td>
<td>Bayer</td>
<td>Bone metastasis</td>
<td>Calcium analogue</td>
</tr>
<tr>
<td>(^{90})Y-loaded glass microspheres</td>
<td>BTG</td>
<td>Hepatic malignancies</td>
<td>Radioembolization of liver microvasculature</td>
</tr>
<tr>
<td>(^{90})Y-loaded resin microspheres</td>
<td>CDH Genetech/Sirtex</td>
<td>Hepatic malignancies</td>
<td>Radioembolization of liver microvasculature</td>
</tr>
<tr>
<td>(^{131})I radioiodine</td>
<td>Jubilant Draximage/Malkincredible</td>
<td>Thyroid cancer</td>
<td>Active uptake through Na–I symporter and storage in follicular cells</td>
</tr>
<tr>
<td>(^{153})[Sm]lexidronam</td>
<td>Lantheus</td>
<td>Cancer bone pain</td>
<td>Binding to hydroxyapatite matrix</td>
</tr>
<tr>
<td>(^{177})Lu-labelled DOTATATE</td>
<td>Novartis/AAA</td>
<td>Neuroendocrine tumours</td>
<td>SSR-mediated binding</td>
</tr>
<tr>
<td>(^{131})[m]MBG</td>
<td>Progenics</td>
<td>Adrenergic receptor(^+) tumours</td>
<td>Active uptake mechanism via the adrenaline transporter and storage in presynaptic neurosecretory granules</td>
</tr>
</tbody>
</table>

\(^a\) Indicates an RPT that is no longer approved.  

Sgouros et al. Nature Reviews/Drug Discovery, 2020
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators\textsuperscript{a}
VISION

A. Imaging-Based Progression-free Survival

- \(^{177}\)Lu-PSMA-617 + standard care
- Standard care alone

No. of Events/No. of Patients:
- \(^{177}\)Lu-PSMA-617 + Standard Care: 254/385, Median: 8.7 mo
- Standard Care Alone: 93/196, Median: 3.4 mo

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29–0.57), P<0.001

No. at Risk:
- \(^{177}\)Lu-PSMA-617 + standard care: 385 362 272 215 182 137 88 71 49 21 6 1
- Standard care alone: 196 119 36 19 14 13 7 7 3 2 0 0
VISION

B  Overall Survival

No. of Events/No. of Patients  Median
177Lu-PSMA-617+ Standard Care  343/551  15.3
Standard Care Alone  187/280  11.3

Hazard ratio for death, 0.62 (95% CI, 0.52–0.74)
P<0.001

No. at Risk
177Lu-PSMA-617+ standard care  551  535  506  470  425  377  332  289  236  166  112  63  36  15  5  2  0
Standard care alone  280  238  203  173  155  133  117  98  73  51  33  16  6  2  0  0  0

Percent of Patients Alive

0  10  20  30  40  50  60  70  80  90  100
0  2  4  6  8  10  12  14  16  18  20  22  24  26  28  30  32

Months since Randomization
Standard care alone
177Lu-PSMA-617+ standard care
Current Approach

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi Y-90 microspheres for treatment of liver metastases
- 200 mCi I-131 mIBG for neuroendocrine tumours
- 200 mCi x 4 for Y-90 DOTATATE of neuroendocrine tumours
- 200 mCi x 4 for Lu-177 DOTATATE for neuroendocrine tumours
- 200 mCi x 4 - 6 for Lu-177 PSMA for prostate cancers
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Empirical chemotherapy paradigm – learning from observation and experience...
# One Size Does Not Fit All

## Absorbed Doses for Tumors and Organs at Risk in $^{177}$Lu PRRT Studies

<table>
<thead>
<tr>
<th>Organ or lesion</th>
<th>No. of patients</th>
<th>Median (Gy/GBq)</th>
<th>Range (Gy/GBq)</th>
<th>Mean ± SD (Gy/GBq)</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red marrow</td>
<td>6</td>
<td>0.02</td>
<td>0.01–0.13</td>
<td>0.07 ± 0.01</td>
<td>Blood</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>0.02</td>
<td>0.01–0.13</td>
<td>0.04 ± 0.02</td>
<td>Blood</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.02</td>
<td>0.01–0.13</td>
<td>0.034 ± 0.030</td>
<td>Blood</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.02</td>
<td>0.01–0.13</td>
<td>0.04 ± 0.02</td>
<td>Blood</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.02</td>
<td>0.01–0.05</td>
<td>0.01 ± 0.05</td>
<td>Blood</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>&lt;=0.07’ (&lt;=0)</td>
<td>0.01–0.05</td>
<td></td>
<td>SPECT</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.04</td>
<td>0.02–0.06</td>
<td></td>
<td>Blood</td>
<td>13</td>
</tr>
<tr>
<td>Kidneys</td>
<td>6</td>
<td>0.88</td>
<td>0.88±0.19</td>
<td></td>
<td>Planar</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>0.90</td>
<td>0.90±0.30</td>
<td></td>
<td>Planar</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.97</td>
<td>0.97±0.24</td>
<td></td>
<td>Planar</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.90</td>
<td>0.90±0.21</td>
<td></td>
<td>SPECT</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.68</td>
<td>0.33–1.65</td>
<td></td>
<td>Planar</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.61</td>
<td>0.27–1.35</td>
<td></td>
<td>SPECT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>0.36</td>
<td>0.36–0.78</td>
<td></td>
<td>Planar</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>1.15’ (0.61)</td>
<td>0.54–2.16’ (0.34–1.82’)</td>
<td>0.57 ± 0.09</td>
<td>Planar</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.62</td>
<td>0.45–17.74</td>
<td></td>
<td>Planar</td>
<td>15</td>
</tr>
<tr>
<td>Tumors</td>
<td>33</td>
<td>3.9</td>
<td>3.9–37.9</td>
<td></td>
<td>Planar</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>3.9</td>
<td>3.9–37.9</td>
<td></td>
<td>Planar</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>6.7</td>
<td>0.1–20</td>
<td></td>
<td>SPECT</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>1.3–4.8</td>
<td>3.41±0.68</td>
<td></td>
<td>Planar</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.14–1.14’ (&lt;=0)</td>
<td>3.41±0.68</td>
<td></td>
<td>SPECT</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.6</td>
<td>0.14–1.14’ (&lt;=0)</td>
<td>3.41±0.68</td>
<td>Planar</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6.8</td>
<td>1.4–23</td>
<td></td>
<td>SPECT</td>
<td>42</td>
</tr>
</tbody>
</table>

*Pretherapeutic.

*Posttherapeutic.

Eberlein et al J Nucl Med 2017; 58:97S–103S
One Size Does Not Fit All

777 $^{177}$Lu-DOTATATE Patients
SPECT/CT 1, 4 and 7 days post injection

Right Kidney

(x 4) = 23 Gy EBRT Limit

Left Kidney

$P(D_{kidney} \leq 23 \text{ Gy}) = 0.85$

Dose (Gy) Matters

**FIGURE 5.** Tumor dose–response relationship for patients with PNETs treated with PRRT using $^{177}$Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B).

Dose (Gy) Matters

154 patients who stopped therapy for reasons other than progression or clinical deterioration
Individual Treatment Planning Improves Survival

hepatocellular carcinoma that was not amenable to surgery or local ablative treatment

Individual Treatment Planning Improves Survival

hepatocellular carcinoma that was not amenable to surgery or local ablative treatment

Individual Treatment Planning Improves Survival

36% of patients down-staged to surgery in personalized dosimetry are versus 4% in standard

These results challenge the interpretation of the previously published negative phase 3 trials, comparing Y-90 microspheres with other treatments, in which personalized dosimetry was not used.

Garin et al. Lancet Gastroenterol Hepatol 2021
Biomarkers

• Select patients most likely to respond
• Avoid toxicity
• Tumor biopsy
• Serum sampling
• Genetic and epigenetic marker analysis
• Methodology/Results Must be rigorously qualified/validated retrospectively or in prospective studies
• Standardized
• Incorporated in the design of clinical trials

Dosimetry

• Select patients most likely to respond
• Avoid toxicity
• Quantitative imaging
• Blood radioactivity counting
• Dose calculation
• Methodology/Results must be rigorously qualified/validated retrospectively or in prospective studies
• Standardized
• Incorporated in the design of clinical trials
Radiopharmaceutical Therapy (RPT) Dosimetry: Main Steps

- **Image Acquisition:** usually at multi time points
  - Planar, Hybrid Planar/SPECT, SPECT, PET
  - Multi time point imaging - Can we reduce the burden to patient/clinic?
- **Image Reconstruction**
- **Volume of interest segmentation**
  - Manual segmentation is tedious/variable. Can we automate?
- **Quantification**
  - Calibration measurements - can we standardize?, incorporate this step into commercial systems?
- **Time - activity fitting or dose-rate fitting**
- **Absorbed dose (AD) estimation**

Courtesy: Yuni Dewaraja
Commercial and Open Source Dosimetry Software

- **Hermes Medical Solutions**: a suite of dosimetry tools for $^{67}\text{Ga}$, $^{123}\text{I}$, $^{131}\text{I}$, $^{111}\text{In}$, $^{81}\text{Kr}$, $^{177}\text{Lu}$, $^{99m}\text{Tc}$, $^{201}\text{Tl}$, $^{166}\text{Ho}$, $^{90}\text{Y}$, and $^{133}\text{Ba}$ (FDA cleared).

- **MIM Software**: image co-registration, automatic organ segmentation (using an FDA-cleared artificial-intelligence autosegmentation platform), dosimetry for several radionuclides, developing 2 methods of single-time-point dosimetry for $^{177}\text{Lu}$ DOTATATE.

- **PLANET Dose** (DOSIsoft): image co-registration, automatic organ segmentation, FDA cleared for $^{90}\text{Y}$-microsphere SIRT and CE-marked for other isotopes ($^{90}\text{Y}$, $^{177}\text{Lu}$, $^{131}\text{I}$ [pending]).

- **Rapid**: quantitative imaging and dosimetry consulting and analysis services and the software, dosimetry calculations for a number of radionuclides, including $^{90}\text{Y}$, $^{99m}\text{Tc}$, $^{111}\text{In}$, $^{123}\text{I}$, $^{131}\text{I}$, $^{201}\text{Tl}$, $^{223}\text{Ra}$, and $^{227}\text{Th}$. A $510k$ application for FDA clearance in development.

- **QDOSE** (ABX-CRO): image co-registration, automatic organ segmentation, dose calculations for 27 commonly used radionuclides, including $^{90}\text{Y}$-microsphere selective internal radiation therapy (SIRT).

- **The GE Dosimetry Toolkit** (GE Healthcare): image co-registration, automatic organ segmentation, dosimetry for $^{131}\text{I}$-iodide thyroid cancer therapy, $^{90}\text{Y}$-SIRT, and $^{177}\text{Lu}$ therapies.

- **PMOD** (PMOD Technologies): automatic organ segmentation generates dosimetry input data that may be directly imported into an OLINDA/EXM case file or an IDAC, version 2.1, file.

- **Simplicit90Y** (Mirada Medical): software package developed for personalized $^{90}\text{Y}$-SIRT planning, voxelwise techniques for pre- and posttreatment dosimetry.

- **RapidSphere**: software tools for $^{90}\text{Y}$-microsphere dosimetry.

- **Voximetry Torch**: dose calculation algorithm in Torch has been benchmarked against the GEANT4 MC code, for multiple isotopes, including $^{90}\text{Y}$, $^{177}\text{Lu}$, $^{131}\text{I}$, and $^{223}\text{Ra}$. It is possible to generate a dosimetry report structured to meet the requirements for complex dosimetry billing codes in the US.

- **Open Dose 3D**: full 3D dosimetry for molecular radiotherapy procedures using multiple time point 3D datasets, either SPECT/CT or PET/CT.

- **MIRD Software Tools** (cell, fit, calc, mc): a suite of free software applications designed and developed to support the medical radiation dose community.
AAPM RPT Subcommittee

Charge

1. Consolidate, disseminate and maintain available information concerning RPT methodologies, dosimetry, science and practice.
2. Establish structures needed for providing guidelines and Standard Operating Procedures (SOPs) for new and existing RPTs such as Task Groups, Working Groups or MPPGs.
3. Take an active role in the education of the AAPM and general radiation oncology community regarding RPT methodologies and clinical practice.
4. Coordinate with stakeholder groups within AAPM, advising them of overlaps and seeking mutual solutions where needed.
5. Coordinate with stakeholder groups outside of AAPM to develop uniform and effective approaches to common problems with regard to RPT. These may include: SNMMI, EANM, ASTRO, ESTRO, ICRU, IAEA, ICRP, ABS, NIST, FDA, IROC, NRC, DOE.

Active Projects

• WG on Radioactive Microspheres
• TG381 - AAPM Recommendations on imaging, dosimetry and quality assurance procedures for Lu-177-based radionuclide therapy
• TG 378 - Safety, treatment planning, and quantitative pre- and post-treatment imaging and dosimetry for hepatic yttrium-90 microsphere therapy
• MPPG 14 Y-90 microsphere radioembolization (TG356)
• AAPM Summer School 2023

Proposed Projects (pending final approval)

• WG on I-131
• WG on alpha-emitters
• TG on Release Criteria
• TG Calibration and Quality Assurance of SPECT/CT and Counting Systems used for Dosimetry-Guided Radiopharmaceutical Therapy
• TG on RPT traceability and dose calibration QA/QC
SNMMI RPT Dosimetry Task Force
co-chairs: George Sgouros and Pat Zanzonico

JNM Dosimetry Supplement Dec 2021

Radiopharmaceutical Dosimetry for Cancer Therapy: From Theory to Practice
Guest editors: Richard L. Wahl, MD, and John Sunderland, PhD

Can the tailoring of drug dosage improve the effectiveness of radiopharmaceutical therapy (RPT) for cancer patients? The Journal of Nuclear Medicine has issued a new supplement addressing both the rapid progress and the challenges in applying patient-specific radiation dosimetry to guide RPT.

Welcome to the SNMMI Lu-177 Dosimetry Challenge 2021

The SNMMI Dosimetry Task Force has the primary goal of advancing the use of dosimetry in radiopharmaceutical therapy (RPT). It has identified the need for harmonization of dosimetry methods as an area of focus. Although efforts to harmonize and standardize internal dosimetry calculations have been made, there has been a lack of large-scale studies to on which to justify recommendations. The Task Force is thus soliciting members of the nuclear medicine community to contribute to the 177Lu Dosimetry Challenge.
Conclusions:

• RPT tsunami is on the way

• Current “one size fits all” approach is suboptimal

• Dosimetry could be considered as a biomarker of “safe” and “effective” treatment.

• Individualized dosimetry-based treatment planning has a potential to improve the outcome, avoid toxicity, and enable combination of RPT with other therapeutical modalities

• RPT dosimetry is gaining traction at relevant professional societies, but faces pushback

• The advantage of Individualized dosimetry-based treatment planning has to be proved in randomized clinical trails

• Involvement of medical physicist is necessary to improve the outcome of theranostics