Physics Requirements for Implementing a Radiopharmaceutical Therapy (RPT) Program: Radiation Safety and QA for Fixed-Activity RPT

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Conflicts of Interest

➢ None
Outline

(Introduction)

➢ Preparation for use of RPTs
➢ Review of Radioisotopes
➢ RPT Administration
➢ Imaging for Safety
➢ Release Criteria

(Summary & Conclusions)
Preparation for use of RPTs
Preparation for use of RPTs

- Key components:
  - Radioactive Materials (RAM) license
  - Personal protective equipment (PPE)
  - Dose Calibrator QA
  - Gamma Camera QA
  - Auto-well counter QA
  - Survey Meter QA
  - Radioactive waste pipeline
Radioactive Materials (RAM) License

- RAM license issued to an institution by agreement state or NRC
- Broad Scope License vs. Specific License
- Radiation Safety Committee
  - (10 CFR 33.13)
  - Radiation Safety Officer (RSO)
  - Representative of management
  - Persons trained in use of byproduct material
  - Administrative power to control procurement, use, and authorized individuals
Personal Protective Equipment

➢ Personal protective equipment is often mandated by states for those working with unsealed sources

  • Gloves
  • Lab Coat
  • Closed shoes
  • Radiation dosimeters

➢ Some PPE is not mandated, but is helpful for abiding by regulations regarding personnel exposure

  • Tongs/forceps for manipulation of high-activity sources
  • Syringe shields, and other various shielded containers
Dose Calibrator QA

- 10 CFR 35.60 - Every dose administered to a patient must be assayed in a properly functioning (and calibrated) dose calibrator
- Should be accurate in the range of 10 µCi - 10 Ci of $^{99mTc}$
- Administered activities falling outside of ± 20% are considered a misadministration (±10% in some states)
- Consider NIST traceability of standard sources
  - $^{57Co}$, $^{137Cs}$, $^{60Co}$, $^{68Ge}$
- NRC Regs
  - Geometry – At time of installation and major service
  - Accuracy – Annually
  - Constancy – Daily
  - Linearity – Quarterly
Auto-Well Counter QA

- Used for high-sensitivity counting of radioactive specimens such as blood, urine, or “wipes” from surveys of removable contamination

- Wipe testing performed in accordance with 10 CFR 35.315, <200 dpm/100cm²

- Quantitation of activity in blood often used for glomerular filtration rate (GFR) testing and marrow dosimetry for RPT

Tests

- Chi-squared
- Energy resolution
- Efficiency
- Energy Calibration
- Background

<table>
<thead>
<tr>
<th>Performance Parameter</th>
<th>IPA Test Name</th>
<th>Baseline Value</th>
<th>Action Level</th>
<th>Tolerance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>Background CPM in counting window</td>
<td>4 CPM</td>
<td>&lt;30 CPM</td>
<td>&lt;100 CPM</td>
</tr>
<tr>
<td>MCA Energy Calibration</td>
<td>Isotope main peak channel number</td>
<td>61.6</td>
<td>± 40%</td>
<td>± 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[37.0, 86.2]</td>
<td>[30.8, 92.4]</td>
</tr>
<tr>
<td>Energy Resolution</td>
<td>Detector Resolution</td>
<td>19.5%</td>
<td>[18.5%]</td>
<td>[17.5%, 20.5%]</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Absolute Detector Efficiency</td>
<td>71.5%</td>
<td>[70.0%]</td>
<td>[68.0%, 73.0%]</td>
</tr>
<tr>
<td>Counting Statistical Performance</td>
<td>Detector Stability Probability</td>
<td>5.5</td>
<td>[2.0%]</td>
<td>[1.5%, 6.0%]</td>
</tr>
</tbody>
</table>
Survey Meter QA

- GM probes for detecting contamination or locating sources
- Ion chamber survey meters for measuring exposure rates, determining the need for shielding, performing release calculations
- NRC 10 CFR 35.61 – Survey meters must be calibrated annually to an accuracy of ±20% on two scales
  - Note: regulations in CFR 34 and 36 (industrial radiography, and irradiators) are slightly different.
Radioactive Waste Pipeline

➢ Activity enters your clinic

➢ There are four ways the activity can ‘leave’ your clinic:
   1. Administer to a patient and send them home (subject to release criteria)
   2. Wait for it to decay (subject to ‘decay in storage’ regulations)
   3. Down the drain (subject to 10 CFR 20.2003)
   4. You arrange for someone to come pick it up

➢ Decay in storage (10 CFR 35.92)
   • Must have a half-life of <120 days
   • Remove all patient-specific labeling
   • Retain until indistinguishable from background
   • Keep a record

➢ Disposal by release into sanitary sewerage (10 CFR 20.2003)
   • Must be readily soluble or readily dispersible
   • Quantity of release is regulated by NRC/Agreement State
<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni53</td>
<td>6.65</td>
</tr>
<tr>
<td>Ni54</td>
<td>165</td>
</tr>
<tr>
<td>Ni55</td>
<td>224</td>
</tr>
<tr>
<td>Ni56</td>
<td>3.20</td>
</tr>
</tbody>
</table>

Review of Radioisotopes
Isotopes

Increasing Clinical Relevance
I-131

- $[^{131}\text{I}]\text{NaI}$, $^{131}\text{I}$-MIBG, various investigational agents
- $T_{1/2} = 8.03$ d
- Beta decay, $E_{\text{ave}}=182$ keV, 100%
- Gamma emission, $E=365$ keV, 82%
  
  Extraneous emissions @ $636$ keV (7%), $723$ keV (2%)
- SPECT imaging with HE collimator
Lu-177

- $^{177}\text{Lu}$-DOTATATE, $^{177}\text{Lu}$-PSMA-617, various investigational agents
- $T_{1/2} = 6.65$ d
- Beta decay, $E_{\text{ave}} = 134$ keV, 100%
- Gamma emission, $E = 208$ keV, 10.4% and 113 keV, 6.2%
- SPECT Imaging with ME Collimator

- Long-lived impurity!
  - $\sim0.1\%$ Lu-177m, $t_{1/2}: 160$ d
  - 200 mCi $^{177}\text{Lu}$ comes with 200 µCi of $^{177m}\text{Lu}$
  - Not dosimetrically consequential, but cannot decay in storage
Y-90

- $^{90}$Y-microspheres, $^{90}$Y-DOTATOC,
- $T_{1/2} = 2.67$ d
- Beta decay, $E_{\text{ave}}=934$ MeV, 100%
- Positron emission, 36 per million decays
- No extraneous gamma emissions, therefore Bremsstrahlung spectrum can be used for SPECT imaging
- PET imaging provides superior quantitative capabilities, due to a lack of scatter correction in Bremsstrahlung SPECT reconstruction
  - High-energy SPECT collimator and a narrow energy window provides the best quantitative performance, however sensitivity suffers
Administration of RPTs: Where? How?
Where?

- Interventional Radiology suite (\(^{90}\)Y-microspheres, intra-arterial PRRT)
- Standard infusion bay (\(^{177}\)Lu-DOTATATE)
- Therapeutic infusion suites (concrete, steel- or Pb-lined rooms)
In-patient vs Out-patient

- Anyone who requires continued medical care
- High-dose $^{131}$I$\text{NaI}$
- $^{131}$I-MIBG
- Other $^{131}$I-based investigational agents

- Any $^{90}$Y treatment, unless post procedure recovery is needed
- Typical $^{131}$I$\text{NaI}$ administrations
- $^{177}$Lu-DOTATATE
- $[^{223}\text{Ra}]\text{RaCl}_2$
Radiation Workers
- 50 mSv/yr to whole body
- 5 mSv over entire pregnancy

Members of the Public
- 1 mSv/yr to whole body
- 20 µSv in any one hour
- Up to 5 mSv/yr in certain cases

Typical design goal
- 20 µSv/wk for uncontrolled spaces
- 100 µSv/wk for controlled spaces

To reduce radiation exposure:
- Limit Time (Free!)
- Increase Distance (Depends)
- Use Shielding (Expensive)
Examples

- 1.5 – 7.0 GBq of $[^{131}\text{I}]\text{NaI}$ commonly used for thyroid cancer patients
- Exposure rate constant for $^{131}\text{I} = 59 \, \mu\text{Sv m}^2/\text{h GBq}$

Calculation parameters:
- Goal: 20 $\mu\text{Sv/wk}$ to maximally exposed individual
- Assume no shielding and occupancy of 0.25
- Two patients per week
- Each patient receives 7.0 GBq
- Biological half-life of 15 h
- Patient self-attenuation: 50%

D = 11 meters (~36 ft) would be sufficient to meet the exposure criteria
<table>
<thead>
<tr>
<th>Radiation type</th>
<th>Most abundant emissions (&gt;10 keV, &gt;0.01%)</th>
<th>Most energetic emissions (&gt;10 keV, &gt;0.01%)</th>
<th>Shielding information (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma &amp; X-ray</td>
<td>364.49 keV (81.2%) 636.99 keV (7.3%) 284.3 keV (6.1%)</td>
<td>722.91 keV (1.8%) 642.7 keV (0.22%) 636.99 keV (7.3%)</td>
<td>Lead: 1&lt;sup&gt;st&lt;/sup&gt; HVL = 3.9, 2&lt;sup&gt;nd&lt;/sup&gt; HVL = 3.1, 1&lt;sup&gt;st&lt;/sup&gt; TVL = 12, 2&lt;sup&gt;nd&lt;/sup&gt; TVL = 17</td>
</tr>
<tr>
<td>Beta(-), Beta(+), electrons</td>
<td>606.31 keV (89.4%) 333.81 keV (7.36%) 45.62 keV (3.5%)</td>
<td>806.87 keV (0.40%) 629.65 keV (0.05%) 606.31 keV (89.4%)</td>
<td>Steel: 1&lt;sup&gt;st&lt;/sup&gt; HVL = 32, 2&lt;sup&gt;nd&lt;/sup&gt; HVL = 14, 1&lt;sup&gt;st&lt;/sup&gt; TVL = 64, 2&lt;sup&gt;nd&lt;/sup&gt; TVL = 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Concrete: 1&lt;sup&gt;st&lt;/sup&gt; HVL = 118, 2&lt;sup&gt;nd&lt;/sup&gt; HVL = 50, 1&lt;sup&gt;st&lt;/sup&gt; TVL = 226, 2&lt;sup&gt;nd&lt;/sup&gt; TVL = 134</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Practical range in glass: 0.9 practically range in plastic: 1.6</td>
</tr>
</tbody>
</table>
Examples

- 1.5 – 7.0 GBq of $[^{131}\text{I}]\text{NaI}$ commonly used for thyroid cancer patients
- Exposure rate constant for $^{131}\text{I} = 59 \mu\text{Sv m}^2/\text{h GBq}$

Calculation parameters:

- Goal: 20 $\mu\text{Sv/wk}$ to maximally exposed individual
- Assume 1” of Pb, $B = 0.0163$
- Occupancy of 0.25
- Two patients per week
- Each patient receives 7 GBq
- Biological half-life of 15 h
- Patient self-attenuation: 50%

- $D = 1.4$ meters (~4.6 ft) would be sufficient to meet the exposure criteria
Shielding ($^{177}$Lu)

- 7.6 µSv m$^2$ / h GBq
- TVL = 2.1 mm Pb

- 1 patient per week, no shielding, 7.4 GBq, 50% self-attenuation, 0.25 occupancy, send patient home on the same day (8 hours of personnel exposure)

- 1.7 m (5.6 ft) sufficient to ensure < 20 µSv of personnel exposure.

- If you’re treating more patients, using higher levels of administered activity, or simply want to reduce exposure - mobile barriers can be used to provide about 1 TVL
How?

- Oral
- Intravenous
- Intraarterial
- Interstitial
Intravenous Administration of RPT

➢ Types of IV catheters
  • Peripheral intravenous line (some risk of extravasation)
  • Peripheral midline catheter (almost no risk of extravasation)
  • Central Line (not used for RPT)
Risk of Extravasation

- Extravasation can range from being a mild or severe complication depending on the volume and medicine administered.

- With RPT, the risk is intrinsically high.

- 5% of $^{177}$Lu-DOTATATE AA extravasated, dwelling in 10 cc of tissue for 24 hours delivers more than 100 Gy…

- Best practice:
  - Attentive technologists
  - Authorized user present and responsive to concerns of techs
  - Flushing lines before and after administration RPT
  - Consider midline catheter in challenging cases
  - If possible, include the site of administration in post-treatment imaging.
Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review

Jochem van der Pol¹ · Stefan Völz¹ · Jan Buerius¹,² · Felix M. Mottaghy¹,²

Table 3 Summary of reported cases of therapeutic radiopharmaceutical extravasation

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients with extravasation</th>
<th>Radiopharmaceutical</th>
<th>Reported extravasated activity [GBq]</th>
<th>Reported administered volume [ml]</th>
<th>Reported estimated tissue dose [Gy]</th>
<th>Symptoms after radiopharmaceutical extravasation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams 2006</td>
<td>1</td>
<td>⁹⁰Y-ibritunomab tiuxetan</td>
<td>0.068–0.136</td>
<td>60</td>
<td>10–20 worst case</td>
<td>Erythema (1d), tenderness (1–4d), bulla (26d), moist desquamation (29d)</td>
</tr>
<tr>
<td>Siebeneck 2008</td>
<td>1</td>
<td>⁹⁰Y-ibritunomab tiuxetan</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Small erythematous area (1w). Progression to 15 × 25 cm erythematous area (4w). Moist desquamation (5w). No healing progression after 8–15w. Skin graft was advised. After 4m start of tissue granulation, with greyish necrotic in the centre size of dime.</td>
</tr>
<tr>
<td>Erken 1991</td>
<td>3</td>
<td>⁶⁷Ga-colloid (radiosynovectomy)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Needle track necrosis. Spontaneous healing (3m)</td>
</tr>
<tr>
<td>Terwinghe 2012</td>
<td>1</td>
<td>⁶⁷Cu-DOTATOC</td>
<td>3.5 (worst case)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Painful and swollen arm (p.i.). No symptoms arose during follow-up (no time indication).</td>
</tr>
<tr>
<td>Minsky 1987</td>
<td>1</td>
<td>³²P-sodium phosphate</td>
<td>0.086</td>
<td>76</td>
<td>5.02</td>
<td>Raised area at infusion site (p.i.).</td>
</tr>
<tr>
<td>Patton 1950</td>
<td>1</td>
<td>⁹⁰Y-hydroxy citrate complex</td>
<td>Not reported</td>
<td>0.2</td>
<td>1000</td>
<td>Ukeration, 2cm in diameter.</td>
</tr>
<tr>
<td>Bonta 2011</td>
<td>1</td>
<td>¹³¹I-metaiodobenzylguanidine</td>
<td>11.1 (worst case)</td>
<td>60</td>
<td>20–40</td>
<td>Forearm swelling (7d). Rash at injection site, 10x5cm (4w). Lesion still “angry looking” (7w), lesion appearance evolved to dry and scaly after corticosteroid cream.</td>
</tr>
<tr>
<td>Kawabe 2013</td>
<td>1</td>
<td>⁸⁹Sr-Strontium chloride</td>
<td>0.00296</td>
<td>30</td>
<td>1.78</td>
<td>Slight burning pain, slight reddening and small circular swelling. No symptoms reported during follow up.</td>
</tr>
</tbody>
</table>

*Whenever available, the time of symptom presentation and other events is printed between brackets, the following abbreviations are used: d days, w weeks, m months, p.i. post injection
Fig. 1 Flowchart describing the protocol in use in Maastricht University Medical Center for management of radiopharmaceutical extravasation.
Imaging for Fixed Activity RPT Administration
Imaging for Fixed Activity-based Administration of RPTs: Why?

- Safety!

- Post-treatment imaging is always performed following $^{90}$Y microsphere administration to confirm hepatic localization

- Detection of extravasation for IV-administered RPTs

- Normal organ dosimetry
  - Required for pre-treatment $^{131}$I-MIBG planning
  - Recommended for post-treatment $^{177}$Lu-DOTATATE safety analysis
Imaging for Fixed Activity-based Administration of RPTs: How?

- Routine quality assurance of gamma cameras – TG177 and accrediting bodies
- Collimator and energy-window selection should be appropriate for the radioisotope
- Recommendations for quantitative SPECT imaging: MIRD 23, 24, 26
- Planar vs. SPECT/CT
  - Patient’s performance status
  - Quantitative accuracy
Release Criteria
When can you release a patient?

10 CFR 35.75 permits the licensee to authorize the release of any individual from its control who has been administered unsealed byproduct material or implants containing byproduct material if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (mSv) (0.5 rem). ¹
When can you release a patient? (Details)

➢ 10 CFR 35.75(b) – you must provide the patient with release instructions

➢ 10 CFR 35.75(c,d) – you must retain a record of the basis for authorizing the release and instructions provided to the patient (3 years minimum)

➢ Methods of release:
  • Based on administered activity
  • Based on exposure rate measurement
  • Based on patient-specific calculations

a. Wash his or her hands frequently.
b. Wash his or her laundry separately from other people’s laundry.
c. Use dedicated or disposable kitchen utensils, and do not share them with others.
d. Use a bathroom reserved exclusively for him or her, if possible.
e. Use disposable gloves and flushable wipes when cleaning.
f. Discard his or her trash separately and hold it to allow for radioactive decay.
g. Sleep alone.
h. Abstain from all forms of intimate contact.
i. Avoid preparing or sharing food with others.
j. Avoid using public transportation, if possible.
k. Minimize the amount of time spent near other people, especially children and pregnant women.

The licensee should instruct family members and caregivers to notify the treating medical facility of a medical emergency or if a patient passes away. The licensee should again tell the patient how to clean up an area contaminated with body fluids (e.g., urine, vomit).
Release criteria: Administered activity or Exposure Rate

<table>
<thead>
<tr>
<th>RADIONUCLIDE</th>
<th>COLUMN 1 ACTIVITY AT OR BELOW WHICH PATIENTS MAY BE RELEASED (GBq)</th>
<th>COLUMN 2 DOSE RATE AT 1 METER, AT OR BELOW WHICH PATIENTS MAY BE RELEASED (mSv/h)</th>
<th>(mrem/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag-111</td>
<td>19</td>
<td>0.08</td>
<td>8</td>
</tr>
<tr>
<td>Au-198</td>
<td>3.5</td>
<td>0.21</td>
<td>21</td>
</tr>
<tr>
<td>Cr-51</td>
<td>4.8</td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>Cu-64</td>
<td>8.4</td>
<td>0.27</td>
<td>27</td>
</tr>
<tr>
<td>Cu-67</td>
<td>14</td>
<td>0.22</td>
<td>22</td>
</tr>
<tr>
<td>Ga-67</td>
<td>8.7</td>
<td>0.18</td>
<td>18</td>
</tr>
<tr>
<td>I-123</td>
<td>6.0</td>
<td>0.26</td>
<td>26</td>
</tr>
<tr>
<td>I-125</td>
<td>0.25</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>I-125 implant</td>
<td>0.33</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>I-131</td>
<td>1.2</td>
<td>0.07</td>
<td>7</td>
</tr>
<tr>
<td>In-111</td>
<td>2.4</td>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td>Ir-192 implant</td>
<td>0.074</td>
<td>0.008</td>
<td>0.8</td>
</tr>
<tr>
<td>P-32</td>
<td>(c)</td>
<td>(c)</td>
<td>(c)</td>
</tr>
<tr>
<td>Pd-103 implant</td>
<td>1.5</td>
<td>0.03</td>
<td>3</td>
</tr>
<tr>
<td>Re-186</td>
<td>28</td>
<td>0.15</td>
<td>15</td>
</tr>
<tr>
<td>Re-188</td>
<td>29</td>
<td>0.20</td>
<td>20</td>
</tr>
<tr>
<td>Se-47</td>
<td>11</td>
<td>0.17</td>
<td>17</td>
</tr>
<tr>
<td>Se-75</td>
<td>0.089</td>
<td>0.005</td>
<td>0.5</td>
</tr>
<tr>
<td>Sm-153</td>
<td>26</td>
<td>0.3</td>
<td>30</td>
</tr>
<tr>
<td>Sm-117m</td>
<td>1.1</td>
<td>0.04</td>
<td>4</td>
</tr>
<tr>
<td>Sr-89</td>
<td>(c)</td>
<td>(c)</td>
<td>(c)</td>
</tr>
<tr>
<td>Te-99m</td>
<td>28</td>
<td>0.58</td>
<td>58</td>
</tr>
<tr>
<td>Tl-201</td>
<td>16</td>
<td>0.19</td>
<td>19</td>
</tr>
<tr>
<td>Y-90</td>
<td>(c)</td>
<td>(c)</td>
<td>(c)</td>
</tr>
<tr>
<td>Yb-169</td>
<td>0.37</td>
<td>0.02</td>
<td>2</td>
</tr>
</tbody>
</table>
APPENDIX B

PROCEDURES FOR CALCULATING DOSES BASED ON PATIENT-SPECIFIC FACTORS

A licensee may release a patient who has been administered a dosage higher than the values listed in Column 1 of Table 1 of this regulatory guide if dose calculations using patient-specific parameters, which are less conservative than the conservative assumptions, show that the total effective dose equivalent to any individual is not likely to be greater than 5 millisieverts (mSv) (0.5 rem).

If the release of a patient is based on a patient-specific calculation that considered the retained activity, an occupancy factor of less than 0.25 at 1 meter, the effective half-life, or shielding by tissue, Title 10 of the Code of Federal Regulations (10 CFR) 35.2075(a) requires the licensee to maintain a record of the basis for authorizing the release.

The following equation can be used to calculate doses:

\[
D(t) = \frac{34.6 \Gamma Q_0 T_p E (1-e^{-\lambda t})}{t^2},
\]

(Equation B-1)

where:
- \(D(t)\) = accumulated dose to time \(t\) in rem
- 34.6 = conversion factor of 24 hours per day times total integration of decay (1.44)
- \(\Gamma\) = exposure rate constant for a point source, R/mCi × hr at 1 centimeter (cm)
- \(Q_0\) = initial activity at the start of the time interval
- \(T_p\) = physical half-life in days
- \(E\) = occupancy factor that accounts for different occupancy times and distances when an individual is near a patient
- \(r\) = distance in centimeters (this value is typically 100 cm)
- \(t\) = exposure time in days
Conclusions

➢ Recent RPT developments represent a significant step forward in terms of patient care.
➢ Physics requirements for RPT programs resemble what has been needed for radioiodine therapy historically, however new radioisotopes and radiopharmaceuticals should be considered individually.
➢ SPECT/CT-based quantitative imaging should play a role in all RPT programs, even those that are administered fixed levels of administered activity clinically.
Thank you!

Questions: stephen-a-graves@uiowa.edu