Unusual Radiation Safety Issues in Nuclear Medicine
From Alphas to Fetuses

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Society of Nuclear Medicine and Molecular Imaging

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Disclosures

• Southern Isotopes
  – Employee
    • FDG Distribution

• Bayer HealthCare Pharmaceuticals
  – Investigator
    • Radium Ra-223 dichloride clinical trials
Educational Objectives

• Objectives of this lecture
  – Restate important details relative to the radiation concerns resulting from administration and handling of Xofigo (radium-223 dichloride)

  – Restate important details relative to radiation concerns in $^{18}$F-FDG PET imaging during pregnancy
XOFIGIO (RADIIUM-223)
Xofigio

- Clinical Usage
- Safety Issues
- Our Experiences
Clinical Utility

- **Xofigo®** (radium Ra 223 dichloride) injection indication
  - Treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.\(^1\)

- **ALSYMPCA Trial**
  - Increased survivability from 11.3 to 14.9 months
  - Increased time without skeletal-related event from 9.8 to 15.6 months

- FDA approved

Kaplan-Meier overall survival curves from the Phase 3 clinical study.\(^1\)
Radium Ra-223 dichloride

• Radium-223
  – Half-life of 11.4 days\textsuperscript{2}
  – Decay energy of 28 MeV\textsuperscript{3}
  – Branching ratios\textsuperscript{3}
    • 95.3% alphas
    • 3.6% betas
    • 1.1% gamma or x-rays
  – Alpha has a range of < 100 $\mu$M
  – Calcium analogue
    • Forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover (such as metastases).
Administrative Dosage

• Dose based on body weight
  – 50 kBq/kg or 1.35 µCi/kg
  – Radioactive concentration of product
    • 1,000 kBq/mL or 27 µCi/mL at reference date
  – One dose per month for six (6) months
  – Decay correction factor to correct for physical decay

\[
\text{Dose (kBq)} = \text{Body Weight in kg} \times 50 \text{ kBq/kg}
\]

\[
\text{Dose (mL)} = \frac{\text{Body Weight in kg} \times 50 \text{kBq/kg}}{\text{Decay Factor} \times 1,000 \text{kBq/mL}}
\]
Decay Factor

- Decay Factor Table (provided with each dose)
  - Notice it’s only in 24 hour increments
  - Dosing uncertainty

<table>
<thead>
<tr>
<th>Days from reference date</th>
<th>Decay Factor</th>
<th>Days from reference date</th>
<th>Decay Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14</td>
<td>2.296</td>
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<td>0.982</td>
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<tr>
<td>-13</td>
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<td>-11</td>
<td>1.914</td>
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<td>1.802</td>
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<td>0.683</td>
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<tr>
<td>-7</td>
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<td>-5</td>
<td>1.330</td>
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<td>-3</td>
<td>1.178</td>
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<td>-1</td>
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<td></td>
<td></td>
<td>14</td>
<td>0.420</td>
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</table>
Radiation Safety Issues

• Radiation Exposure to Patients
  – Dosimetry
  – Excretion
  – Patient Instructions

• Radiation Exposure to Staff
  – Inhalation
  – Needle Stick
  – Ingestion
  – Topical Exposure

• Dose Calibration
Radiation Exposure to Patients

• Radium-223 is rapidly cleared from the blood
  – 15 minutes post-administration, 20% in blood
  – At 4 hours, 4% in blood
  – At 24 hours, < 1% in blood
# Radiation Exposure to Patients

## Table of Absorbed Organ Dose

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Mean (Gy/MBq)</th>
<th>Mean (rad/mCi)</th>
<th>Coefficient of Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.00012</td>
<td>0.44</td>
<td>56</td>
</tr>
<tr>
<td>Brain</td>
<td>0.00010</td>
<td>0.37</td>
<td>80</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.00005</td>
<td>0.18</td>
<td>120</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>0.00023</td>
<td>0.85</td>
<td>14</td>
</tr>
<tr>
<td>Lower large intestine wall</td>
<td>0.04645</td>
<td>171.88</td>
<td>83</td>
</tr>
<tr>
<td>Small intestine wall</td>
<td>0.00726</td>
<td>26.87</td>
<td>45</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.00014</td>
<td>0.51</td>
<td>22</td>
</tr>
<tr>
<td>Upper large intestine wall</td>
<td>0.03232</td>
<td>119.58</td>
<td>50</td>
</tr>
<tr>
<td>Heart wall</td>
<td>0.00173</td>
<td>6.40</td>
<td>42</td>
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<td>Kidneys</td>
<td>0.00320</td>
<td>11.86</td>
<td>36</td>
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<tr>
<td>Liver</td>
<td>0.00298</td>
<td>11.01</td>
<td>36</td>
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<tr>
<td>Lungs</td>
<td>0.00007</td>
<td>0.27</td>
<td>90</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.00012</td>
<td>0.44</td>
<td>41</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.00049</td>
<td>1.80</td>
<td>40</td>
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<tr>
<td>Pancreas</td>
<td>0.00011</td>
<td>0.41</td>
<td>43</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.03879</td>
<td>513.51</td>
<td>41</td>
</tr>
<tr>
<td>Osteogenic cells</td>
<td>1.15206</td>
<td>4262.60</td>
<td>41</td>
</tr>
<tr>
<td>Skin</td>
<td>0.00007</td>
<td>0.27</td>
<td>79</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.00009</td>
<td>0.33</td>
<td>54</td>
</tr>
<tr>
<td>Testes</td>
<td>0.00008</td>
<td>0.31</td>
<td>59</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.00006</td>
<td>0.21</td>
<td>109</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.00007</td>
<td>0.26</td>
<td>96</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>0.00403</td>
<td>14.90</td>
<td>63</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.00026</td>
<td>0.94</td>
<td>28</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.02311</td>
<td>85.50</td>
<td>16</td>
</tr>
</tbody>
</table>
Radiation Exposure to Patients

• Excretion
  – 63% of dose is excreted within one week
  – Fecal excretion is main route
    • At 48 hours post-injection
      – Cumulative fecal excretion was 13% (range 0-34%)
      – Cumulative urine excretion was 2% (range 1-5%)
Patient Instructions

• ‘Patients should adhere to good personal hygiene practices while receiving radium 223’
• Patients should flush the toilet multiple times after each use.
• Soiled clothing should be washed promptly and separately
• Caregivers should wear gloves
• ‘There are no restrictions regarding contact with other people after receiving radium 223’
Staff Radiation Safety

- Radiation Exposure to Staff
  - Patient
  - Inhalation
  - Needle Stick
  - Ingestion
  - Topical Exposure
Exposure from patient

• Small doses
  – Typical treatment <8,000 kBq (216 μCi)
• Radium goes to bones
  – Attenuation
• Short range of alpha
  – 100 μM
• External exposure very small!
Inhalation Risk

• Resulting from spill or leakage
  – Radium 223 dichloride is not volatile
  – Radon-219 is in the decay chain
    • Radon is a serious inhalation risk
    • Radon 219 half life (4 sec) is much shorter than the diffusion time to come out of solution
  – Highly unlikely for significant migration of Radon 219 from radium 223

  – Experimental Data
    • No loss of activity from radium 223 over time
    • No significant release of radon 219 was observed
### Oral Ingestion

- Absorption from gastrointestinal tract is unknown
  - Pharmacokinetic properties are expected to follow IV route
  - Radium 223 is not metabolized
- There is no specific antidote
- Calculated doses are very low
- Probability of long term damage is considered to be very low!

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose equivalent (Sv/Bq)</th>
<th>Sv</th>
<th>TD 5/5 External Beam Tolerance Dose (Gy)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Wall</td>
<td>1.21E-08</td>
<td>6.05E-04</td>
<td>65</td>
</tr>
<tr>
<td>Bone Surface</td>
<td>3.08E-06</td>
<td>1.54E-01</td>
<td>60</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>1.92E-06</td>
<td>9.6E-94</td>
<td>50</td>
</tr>
<tr>
<td>Small Intestine Wall</td>
<td>2.57E-08</td>
<td>1.29E-03</td>
<td>40</td>
</tr>
<tr>
<td>Upper Large Intestine Wall</td>
<td>1.16E-07</td>
<td>5.8E-03</td>
<td>40</td>
</tr>
<tr>
<td>Lower Large Intestine Wall</td>
<td>2.19E-07</td>
<td>1.46E-02</td>
<td>45</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8.03E-09</td>
<td>4.02E-04</td>
<td>23</td>
</tr>
<tr>
<td>Liver</td>
<td>1.41E-07</td>
<td>7.05E-03</td>
<td>30</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>2.86E-07</td>
<td>1.43E-02</td>
<td>2.5</td>
</tr>
<tr>
<td>Spleen</td>
<td>8.57E-09</td>
<td>4.29E-04</td>
<td>N/A</td>
</tr>
<tr>
<td>Testes</td>
<td>1.19E-08</td>
<td>5.95E-04</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Organ doses for an unintended oral intake of 50 kBq of radium-223. Comparison to the tolerance doses from external beam irradiation. *Dose at which there is a 5% probability of complication within 5 years
Needle Stick

- Amount of radium 223 in the needle is tiny
  - Total dose < 200µCi
- If patient dose is administered into perivenous tissue
  - Local effects
  - Will diffuse into bloodstream
  - No significant adverse effects expected based on pre-clinical data
Topical Exposure

• Proper protective clothing
  – Lab coats, gloves, etc.
  – Ensure only a very small amount could possibly be involved in direct skin exposure

• Assume a drop of 50 µL containing 50 kBq contacts 10 cm² of skin for 1 hour

\[
\left(2.0 \times 10^{-10} \text{ Sv} \left( \frac{\text{cm}^2}{\text{Bq s}} \right) \right) \times \frac{50 \text{ kBq} \times 3600 \text{ s}}{10 \text{ cm}^2} = 3.6 \text{ mSv (360 mrem)}
\]

• If contamination remained for 8 hours, only 2900 mrem
• Use 0.1 M ethylene diamine tetra acetate (EDTA) to remove contamination
Dose Calibration

• Radium 223 is not currently a factory calibrated isotope

• Bayer provides a procedure
  – Will send you NIST traceable standard
  – User has to find the proper dial setting
Our Experiences

• Regulatory
• Dose Calibration
• Radiation Safety
Regulatory Experience

• Louisiana is an agreement state
  – LA DEQ Issues
    • Inhalation during preparation
      – Fume hood required
      – Not applicable to sites receiving dose from central pharmacy
    • Bioassays of staff
    • Our center was diagnostic, this was our first therapy
      – Written directive
      – Administration checklist
Dose Calibration

• Bayer calibration procedure
  – Uses 24 hour increments from reference date

• Precision between calibrators
  – Radiopharmacy
  – Clinic
  – Calibrated on different days
    • More importantly different time of day
  – Calibrators read consistently but inaccurately
    • Depending on facility, could be as much as 6%
Radiation Safety

• Dose preparation
  – Tedious, but no data suggesting increased exposure to pharmacy staff

• Administration
  – No data suggesting increased exposure to CNMTs
  – No issues with patient contact
  – No spills or accidental contact
  – SOP’s required for administration
    • Written directive
    • Final dose calculation safety check
Xofigio Radiation Safety Summary

• Radiopharmaceutical therapies are novel for most imaging centers
  – Long-lived isotopes
  – Regulatory scrutiny compared to diagnostic
• Radiation safety concerns are minimal for staff
• SOP’s should be in place in the event of an incident.
PREGNANCY AND $^{18}$F-FDG-PET
Cancer and Pregnancy

• Cancer occurs in approximately 1 in 1000 pregnant women\textsuperscript{5}  
  – Breast, Cervix, Thyroid, Ovarian, Hodgkin’s Disease, Melanoma\textsuperscript{6}  
  – Imaging is a vital component for management/treatment of cancer  
    • Pregnant women are no different
$^{18}$F-FDG-PET and Pregnancy

- $^{18}$F-FDG-PET is a powerful tool for cancer treatment
- Lack of available data on $^{18}$F-FDG-PET and fetal risk
  - Fetal exposure ‘frightening and complicated’ issue
  - No prospective studies because of ethical concerns
  - Even if physician recommended PET imaging, patient may not consent
\(^{18}\text{F-FDG PET and Pregnancy}\)

- Only a few published case reports (mostly accidental exposure)
- May be inappropriate to withhold PET imaging in some cases
- Takalkar \textit{et al} \(^7\) published largest cohort to date
Cohort Data

• 5 pregnant women (one twice for 6 data points)
  – 4 were known pregnancies
    • 6-30 weeks of gestation
  – All biopsy-proven diagnosis
  – Extensive counseling
  – Obtained consent
  – Special imaging protocol
Imaging Protocol

- 5 mCi injected dose
- IV and oral hydration
  - Patients voided on average 4 times during uptake period
- 90 minute uptake period
- GE Healthcare Discovery LS-4
  - Ge-68 transmission scan for attenuation purposes
  - 6-7 min/bed (30-42 min total scan)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnancy Protocol</th>
<th>Standard Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injected Dose (mCi)</td>
<td>4.7 – 9.2</td>
<td>15</td>
</tr>
<tr>
<td>Time per Bed (min)</td>
<td>6-7</td>
<td>5</td>
</tr>
<tr>
<td>Attenuation Correction</td>
<td>Ge-68</td>
<td>CT</td>
</tr>
</tbody>
</table>
Fetal Dose Calculations

• Fetal dose assessed for each patient
  – Fetal volume (cm$^3$)
  – Average concentration (mCi/mL)
  – Manual ROI
  – International Commission on Radiological Protection (ICRP) publication 106$^8$
  – OLINDA/EXM$^9$ - standard bladder-voiding module
  – SAAMII – using data driven bladder-voiding data
30 year old woman with history of juvenile laryngeal papillomatosis and lung cancer

34 year old woman, 28 weeks pregnant. Recently diagnosed with squamous cell carcinoma of cervix
**Fetal Dose**

- Fetus was clearly delineated (except during early pregnancy)
  - No focal uptake in fetus
- All patients delivered healthy infants with no visible abnormalities

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Stage of Gestation (weeks)</th>
<th>Administered Activity (MBq)</th>
<th>Average observed concentration in fetus (kBq/mL)</th>
<th>Total dose to fetus (mGy) 2-h voids</th>
<th>Total Dose to fetus (mGy) – Irregular voiding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>~6</td>
<td>583</td>
<td>16.8</td>
<td>11.4</td>
<td>9.04</td>
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<tr>
<td>2</td>
<td>18</td>
<td>200</td>
<td>1.98</td>
<td>2.06</td>
<td>1.43</td>
</tr>
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<td>3</td>
<td>25</td>
<td>337</td>
<td>2.96</td>
<td>2.49</td>
<td>2.10</td>
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<tr>
<td>4</td>
<td>28</td>
<td>174</td>
<td>2.31</td>
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<td>5</td>
<td>30</td>
<td>229</td>
<td>2.86</td>
<td>2.68</td>
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</tr>
<tr>
<td>6</td>
<td>23</td>
<td>181</td>
<td>2.56</td>
<td>1.32</td>
<td>1.10</td>
</tr>
</tbody>
</table>

This dose is from administered radiopharmaceutical alone. Fetal radiation dose from transmission scanning with 68Ge rod source is negligible, and hence values in this table represent effective fetal radiation dose for 18F-FDG PET–only scans. However, because most PET scanners are now PET/CT scanners and may not have option to be operated in PET-only mode, total fetal radiation exposure from 18F-FDG PET/CT would be additional 6–14 mGy from CT portion of study (this radiation dose depends on CT protocol used during PET/CT study).
Comparison to previous data

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Stage of Gestation (wk)</th>
<th>Our Data</th>
<th>Stabin et al ¹⁰</th>
<th>Zanotti-Fregonara et al ¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>18</td>
<td>0.0023</td>
<td>0.019</td>
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<td>3</td>
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<td>6</td>
<td>23</td>
<td>0.0206</td>
<td>0.064</td>
<td></td>
</tr>
</tbody>
</table>

Time-integrated activity (Bq-h/Bq). Integrals are Bq-h in fetus per Bq administered to mother. Early pregnancy model was used for patient 1, 3-mo-pregnant female model for patient 2, and 6-mo model for all others, because these most closely matched their state of gestation. Dose from study of Zanotti-Fregonara et al. was reasonable to use for comparisons with dose to patient, because patients were at similar stages of gestation. Because fetus of patient 1 was at early gestational age and not well visualized, that patient was omitted from this comparison.
Summary of Fetal Dose

- Fetal volumes correlated well to expected fetal volumes based on MRI and US
- Calculated fetal dose as 1.1 to 2.43 mGy
  - Significantly lower than threshold for fetal deterministic effects (100-600 mGy)$^{12}$
- Calculated dose based on imaging is less than existing estimates
Imaging Protocol Summary

- As low of injected dose as possible (~ 5 mCi)
- Hydrate patient
  - Bladder is most significant source of fetal exposure
- Long uptake time (~ 90 min)
  - Allows more voiding, improves Signal to Noise
- Increase imaging time (~20-40%)
- CT is significant portion of fetal exposure
  - CT acquisition parameters should be as low-dose as possible
\( ^{18}\)F-FDG-PET in Pregnancy Summary

- Fetal exposure from \( ^{18}\)F-FDG-PET is low
- Fetal exposure from \( ^{18}\)F-FDG-PET should be minimized by careful modification of imaging protocol
- The benefits of \( ^{18}\)F-FDG-PET to the mother can, when medically necessary, outweigh the risk to fetus.
END
References (in order of appearance)

2. - Data on file. Radium 223 chloride Ridsk assessment and responses to NRC questions