Unusual Radiation Safety Issues in Nuclear Medicine

From Alphas to Fetuses

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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

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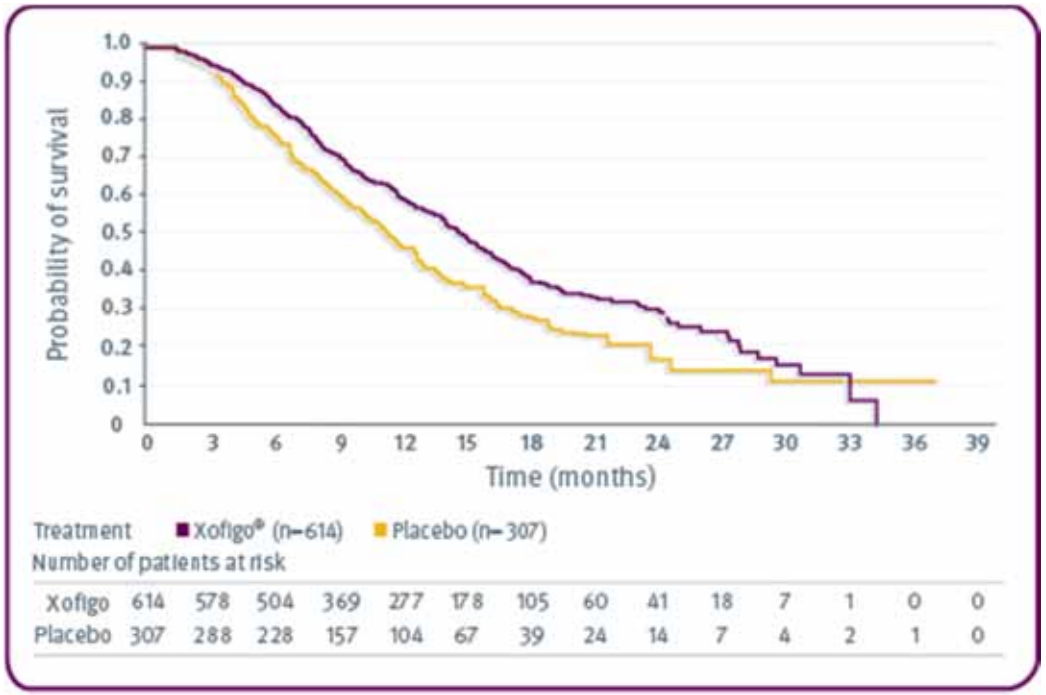
XOFIGIO (RADIUM-223)

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]

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Radium Ra-223 dichloride

- Radium-223
  - Half-life of 11.4 days[2]
  - Decay energy of 28 MeV[3]
  - Branching ratios[3]
    - 95.3% alphas
    - 3.6% betas
    - 1.1% gamma or x-rays
  - Alpha has a range of < 100 µM
  - Calcium analogue
    - Forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover (such as metastases).

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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

$$\text{Dose (kBq)} = \text{Body Weight in kg x 50 kBq/kg}$$

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

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Decay Factor

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

Days from reference date	Decay Factor	Days from reference date	Decay Factor
-14	2.296	0	0.982
-13	2.161	1	0.925
-12	2.034	2	0.870
-11	1.914	3	0.819
-10	1.802	4	0.771
-9	1.696	5	0.725
-8	1.596	6	0.683
-7	1.502	7	0.643
-6	1.414	8	0.605
-5	1.330	9	0.569
-4	1.252	10	0.536
-3	1.178	11	0.504
-2	1.109	12	0.475
-1	1.044	13	0.447
		14	0.420

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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

Absorbed organ dose			
Target organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of variation (%)
Adrenals	0.00012	0.44	56
Brain	0.00010	0.37	80
Breasts	0.00005	0.18	120
Gallbladder wall	0.00023	0.85	14
Lower large intestine wall	0.04645	171.88	83
Small intestine wall	0.00726	26.87	45
Stomach wall	0.00014	0.51	22
Upper large intestine wall	0.03232	119.58	50
Heart wall	0.00173	6.40	42
Kidneys	0.00320	11.86	36
Liver	0.00298	11.01	36
Lungs	0.00007	0.27	90
Muscle	0.00012	0.44	41
Ovaries	0.00049	1.80	40
Pancreas	0.00011	0.41	43
Red marrow	0.13879	513.51	41
Osteogenic cells	1.15206	4262.60	41
Skin	0.00007	0.27	79
Spleen	0.00009	0.33	54
Testes	0.00008	0.31	59
Thymus	0.00006	0.21	109
Thyroid	0.00007	0.26	96
Urinary bladder wall	0.00403	14.90	63
Uterus	0.00026	0.94	28
Whole body	0.02311	85.50	16

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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

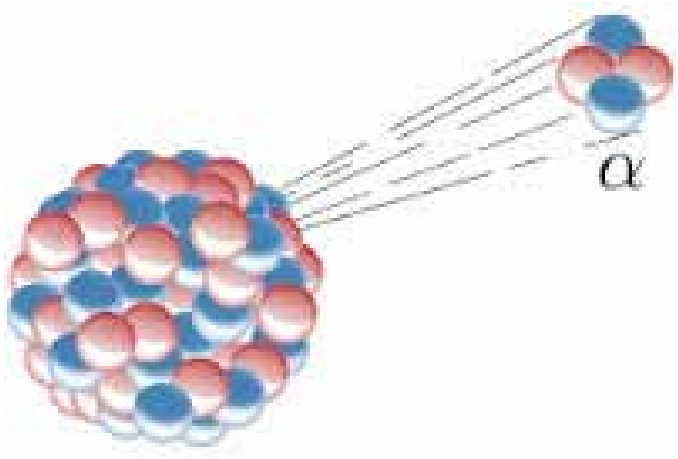
- ‘Patients should adhere to good personal hygiene practices while receiving radium 223’
- Patients should flush the toilet multiple times after each use.
- Soiled clothing should be washed promptly and separately
- Caregivers should wear gloves
- ‘There are no restrictions regarding contact with other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



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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[4]
    - 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!

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

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 blood stream
  - No significant adverse effects expected based on pre-clinical data

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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 cm^2 of skin for 1 hour

$$\left(2.0X10^{-10}\ Sv\frac{cm^2}{Bqs}\right) x \frac{50\ kBq\ x\ 3600\ s}{10\ cm^2} = 3.6\ \text{mSv (360 mrem)}$$

- 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

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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%

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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

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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[5]
  - Breast, Cervix, Thyroid, Ovarian, Hodgkin's Disease, Melanoma[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}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 *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

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Imaging Protocol

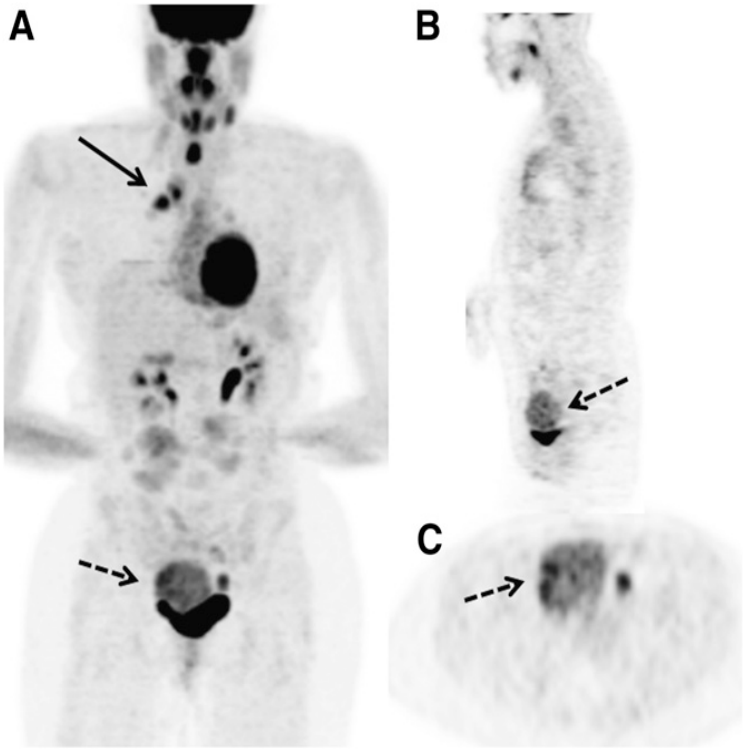
- 5 mCi injected dose
- IV and oral hydration
  - Patients voided on average 4 times during uptake period
- 90 minute uptake period
- GE Healthcare Discovery LS-4
  - Ge-68 transmission scan for attenuation purposes
  - 6-7 min/bed (30-42 min total scan)

Parameter	Pregnancy Protocol	Standard Protocol
Injected Dose (mCi)	4.7 – 9.2	15
Time per Bed (min)	6-7	5
Attenuation Correction	Ge-68	CT

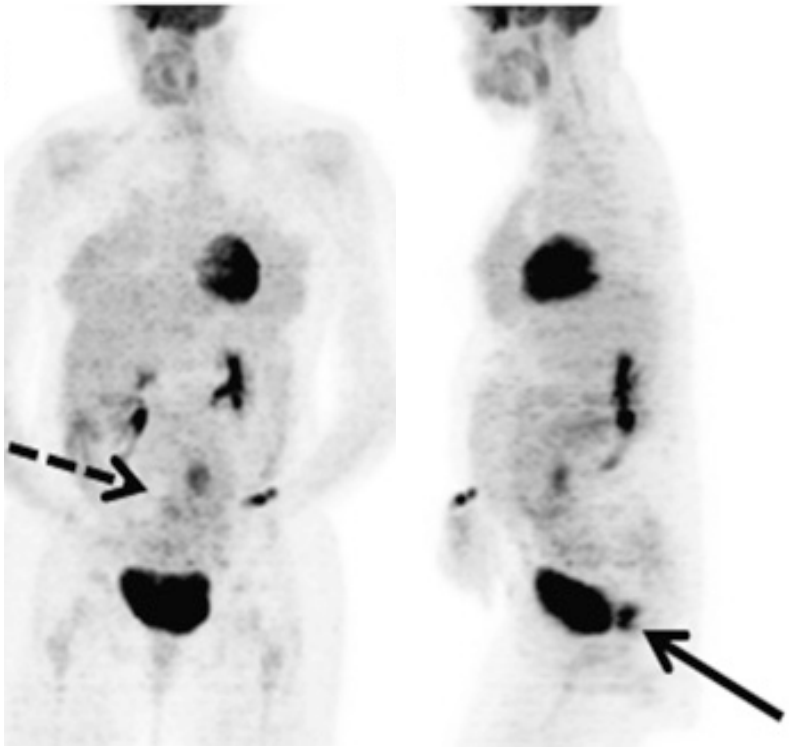
Fetal Dose Calculations

- 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

Images



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

Patient Number	Stage of Gestation (weeks)	Administered Activity (MBq)	Average observed concentration in fetus (kBq/mL)	Total dose to fetus (mGy) 2-h voids	Total Dose to fetus (mGy) – Irregular voiding
1	~6	583	16.8	11.4	9.04
2	18	200	1.98	2.06	1.43
3	25	337	2.96	2.49	2.10
4	28	174	2.31	1.21	1.01
5	30	229	2.86	2.68	2.43
6	23	181	2.56	1.32	1.10

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 ^{18}F-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 ^{18}F-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

Patient Number	Stage of Gestation (wk)	Our Data	Stabin *et al* [10]	Zanotti-Fregonara *et al* [11]
2	18	0.0023	0.019	0.00351
3	25	0.0223	0.064	
4	28	0.0187	0.064	
5	30	0.0518	0.064	
6	23	0.0206	0.064	

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

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