

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

Stephen A. Graves, PhD

Department of Radiology
Department of Radiation Oncology
Department of Biomedical Engineering
University of Iowa



Conflicts of Interest

➤ None



Outline

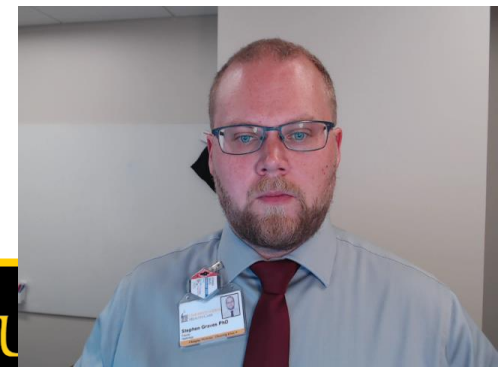
(Introduction)

- 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

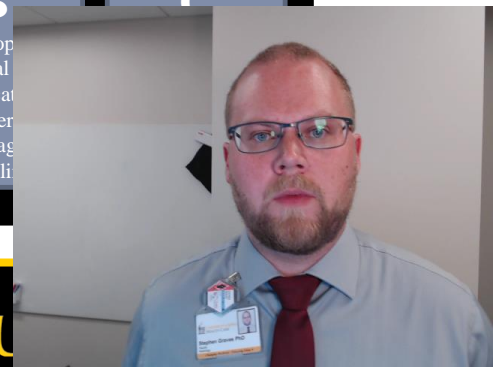
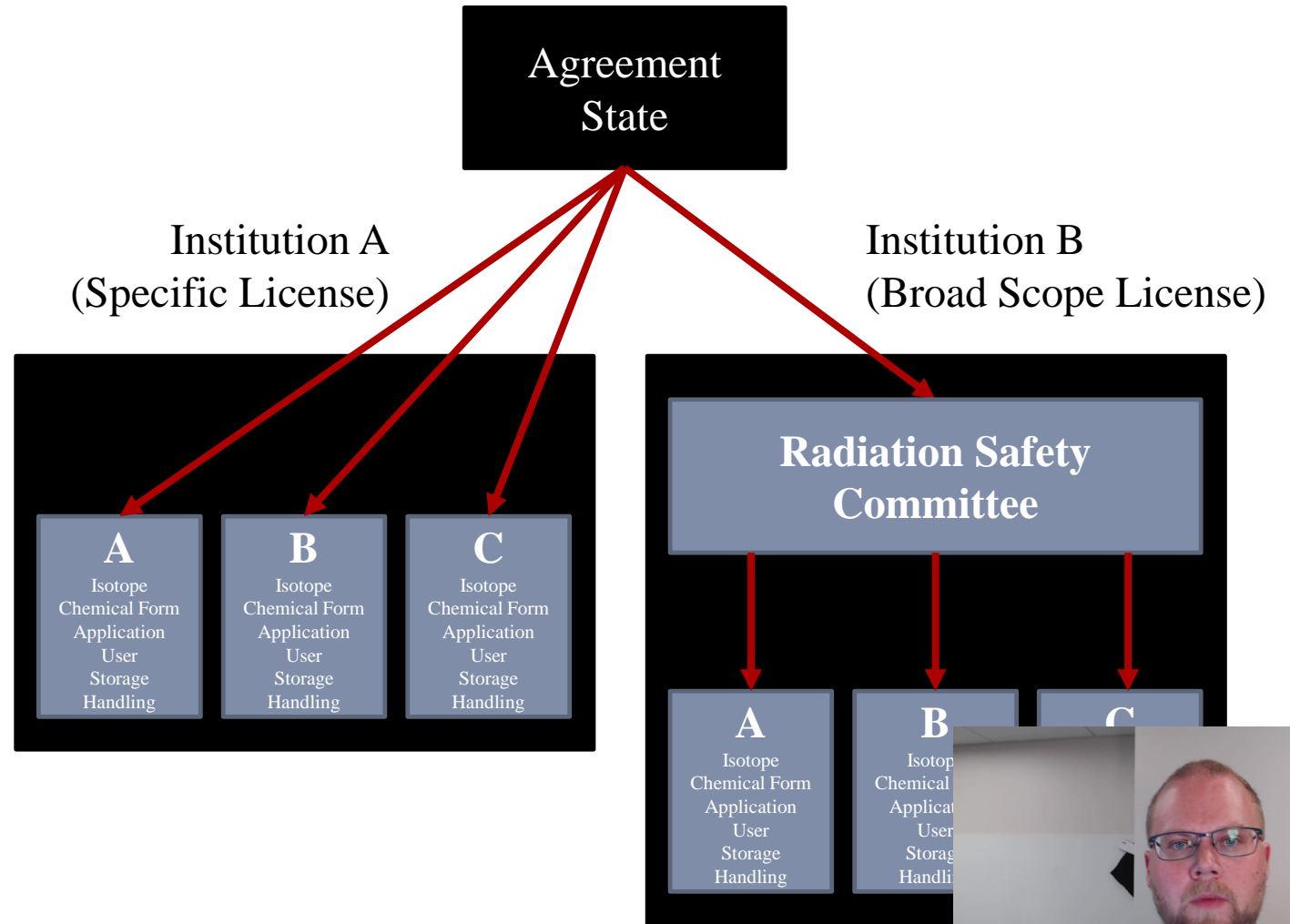
➤ Key components:

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



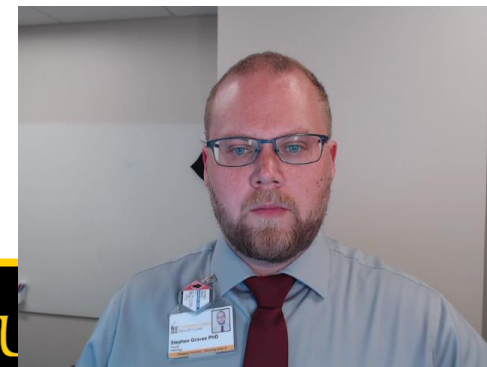
Radioactive Materials (RAM) License

- 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

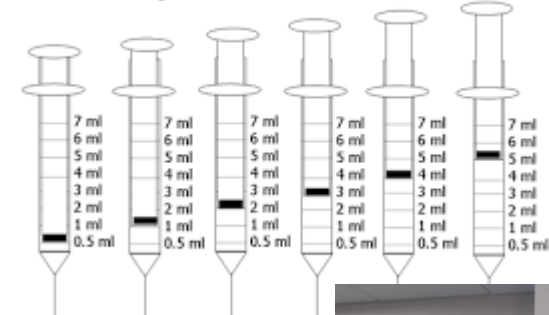


Dose Calibrator QA

- 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 $^{99\text{m}}\text{Tc}$
- Administered activities falling outside of $\pm 20\%$ are considered a misadministration ($\pm 10\%$ in some states)
- Consider NIST traceability of standard sources
 - ^{57}Co , ^{137}Cs , ^{60}Co , ^{68}Ge
- NRC Regs
 - Geometry – At time of installation and major service
 - Accuracy – Annually
 - Constancy – Daily
 - Linearity – Quarterly



Geometry Test: 25 mCi of Tc-99m



Auto-Well Counter QA

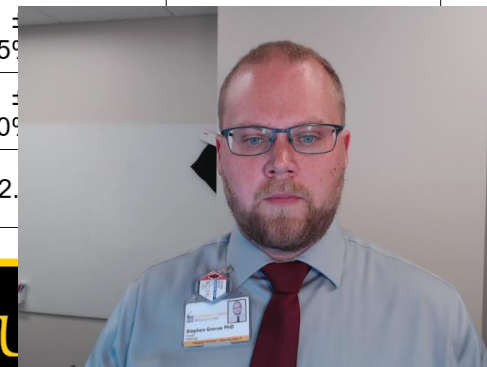
- Used for high-sensitivity counting of radioactive specimens such as blood, urine, or “wipes” from surveys of removable contamination
- Wipe testing performed in accordance with 10 CFR 35.315, <200 dpm/100cm²
- Quantitation of activity in blood often used for glomerular filtration rate (GFR) testing and marrow dosimetry for RPT

➤ Tests

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



Performance Parameter	IPA Test Name	Baseline Value	Action Level	Tolerance Level
Background	Background CPM in counting window	4 CPM	<30 CPM	<100 CPM
MCA Energy Calibration	Isotope main peak channel number	61.6	± 40% [37.0, 86.2]	± 50% [30.8, 92.4]
Energy Resolution	Detector Resolution	19.5%	[18.5%	
Sensitivity	Absolute Detector Efficiency	71.5%	[70.0%	
Counting Statistical Performance	Detector Stability Probability	5.5	[2.	



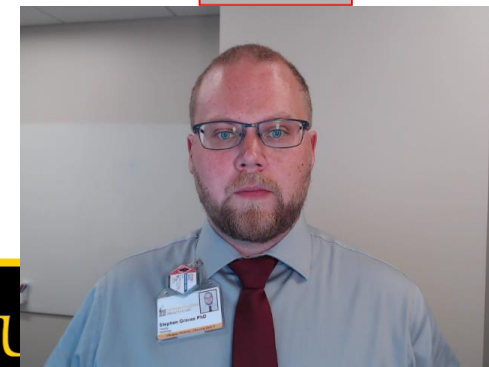
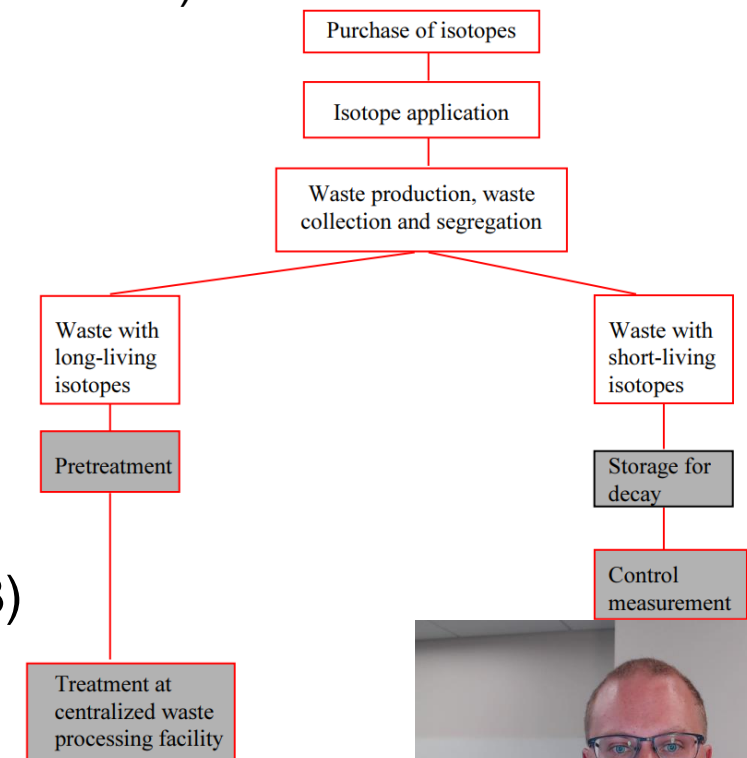
Survey Meter QA

- 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 $\pm 20\%$ on two scales
 - Note: regulations in CFR 34 and 36 (industrial radiography, and irradiators) are slightly different.

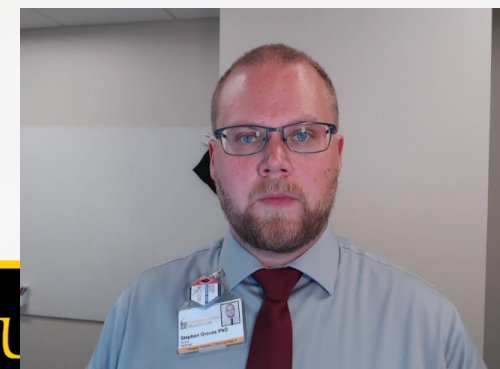


Radioactive Waste Pipeline

- 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



Review of Radioisotopes



Isotopes

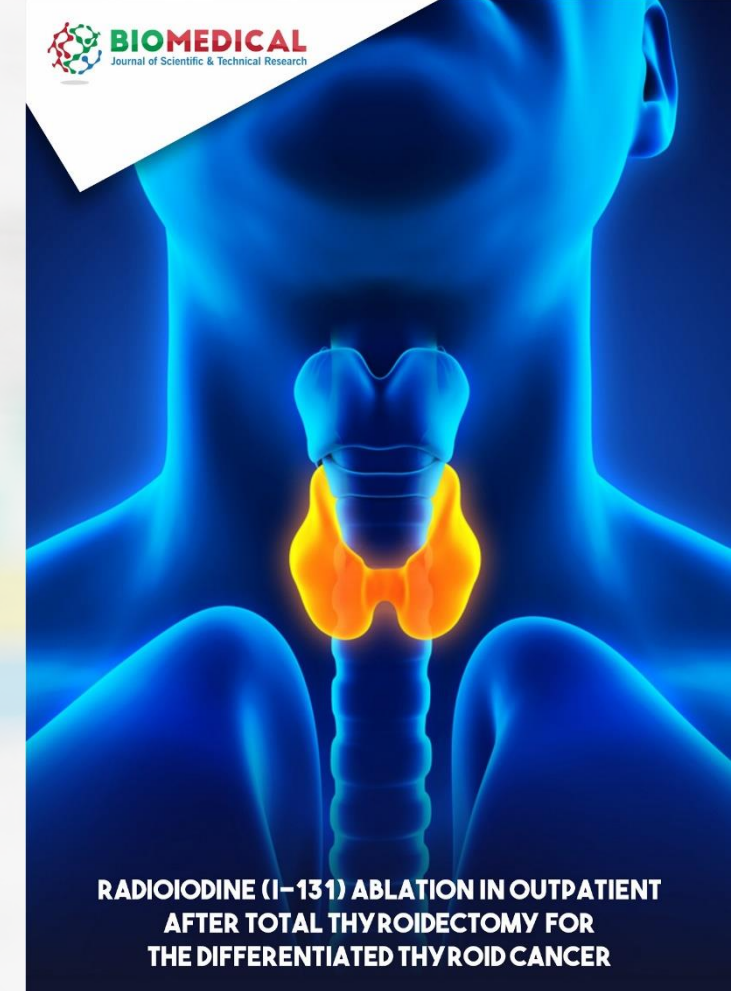
Imaging	$^{51/52}\text{Mn}$	^{61}Cu	^{89}Zr	^{86}Y	^{13}N	^{15}O	^{111}In	^{82}Rb	^{11}C	^{68}Ga	$^{99\text{m}}\text{Tc}$	^{18}F
Imaging/Therapy	^{197}Hg	$^{55/58\text{m}}\text{Co}$	$^{72/77}\text{As}$	$^{44/47}\text{Sc}$	$^{64/67}\text{Cu}$	$^{203/212}\text{Pb}$	^{166}Ho	^{153}Sm	^{177}Lu	$^{123/124/131}\text{I}$	^{90}Y	
Therapy	$^{119\text{m}}\text{Sn}$	^{213}Bi	^{211}At	^{227}Th	^{142}Pr	^{225}Ac	^{223}Ra					

→
Increasing Clinical Relevance

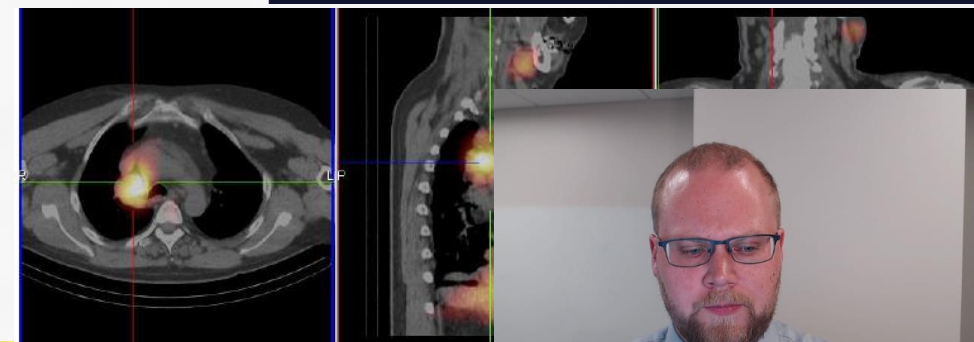
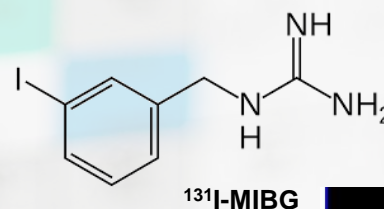


I-131

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

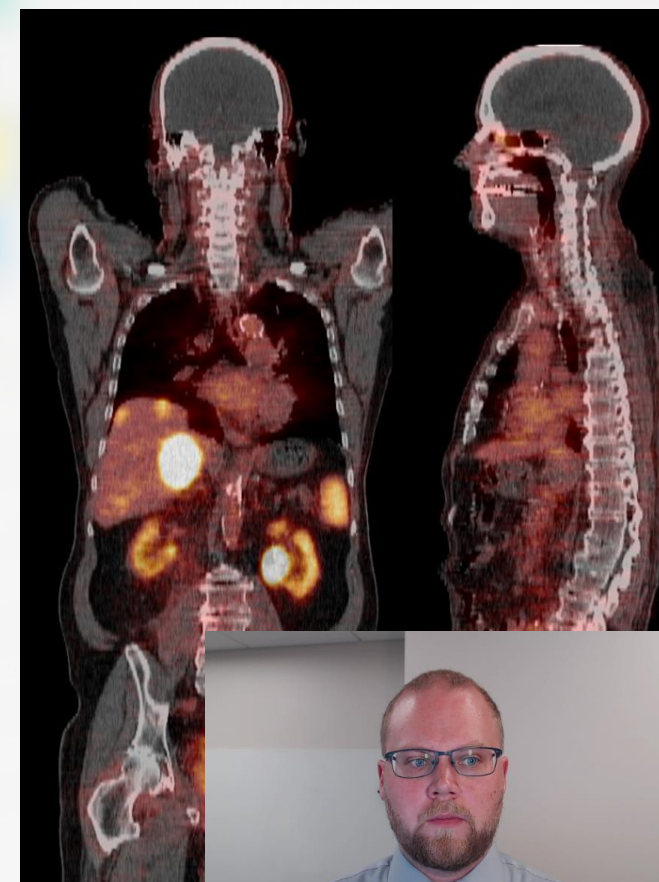
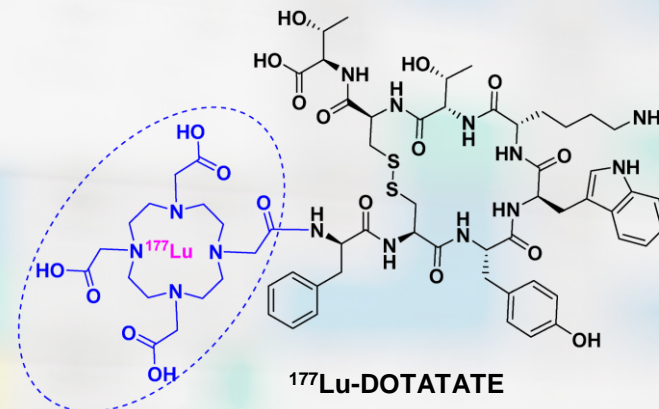


RADIOIODINE (I-131) ABLATION IN OUTPATIENT AFTER TOTAL THYROIDECTOMY FOR THE DIFFERENTIATED THYROID CANCER



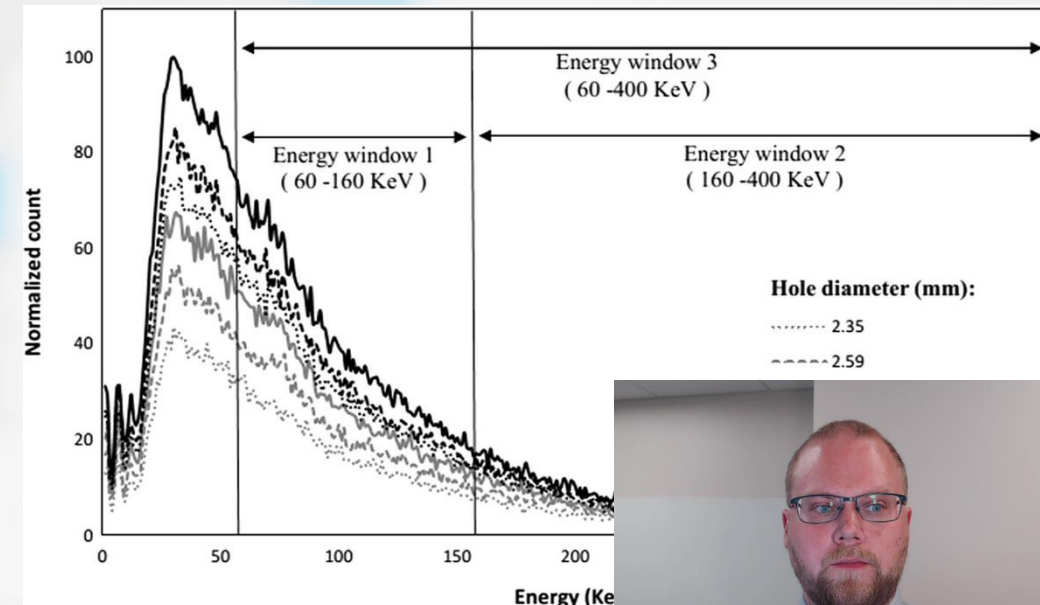
Lu-177

- ^{177}Lu -DOTATATE, ^{177}Lu -PSMA-617, various investigational agents
- $T_{1/2} = 6.65 \text{ d}$
- Beta decay, $E_{\text{ave}} = 134 \text{ keV}$, 100%
- Gamma emission, $E = 208 \text{ keV}$, 10.4% and 113 keV , 6.2%
- SPECT Imaging with ME Collimator
- Long-lived impurity!
 - ~0.1% Lu-177m, $t_{1/2}$: 160 d
 - 200 mCi ^{177}Lu comes with 200 μCi of $^{177\text{m}}\text{Lu}$
 - Not dosimetrically consequential, but **cannot decay in storage**



Y-90

- ^{90}Y -microspheres, ^{90}Y -DOTATOC,
- $T_{1/2} = 2.67 \text{ d}$
- Beta decay, $E_{\text{ave}} = 934 \text{ MeV}$, 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?

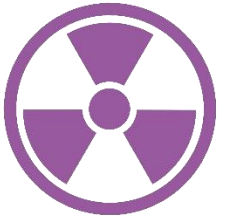


Where?

- 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



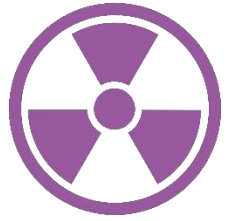
- Anyone who requires continued medical care
- High-dose [^{131}I]NaI
- ^{131}I -MIBG
- Other ^{131}I -based investigational agents



- Any ^{90}Y treatment, unless post procedure recovery is needed
- Typical [^{131}I]NaI administrations
- ^{177}Lu -DOTATATE
- [^{223}Ra]RaCl₂

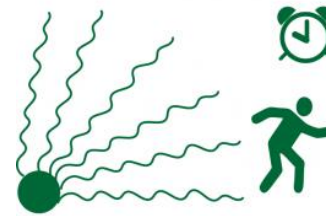


Shielding Goals



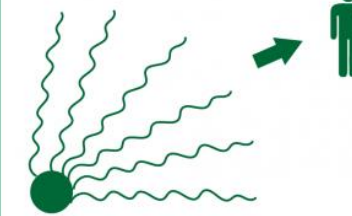
- Radiation Workers
 - 50 mSv/yr to whole body
 - 5 mSv over entire pregnancy
- Members of the Public
 - 1 mSv/yr to whole body
 - 20 μ Sv in any one hour
 - Up to 5 mSv/yr in certain cases
- Typical design goal
 - 20 μ Sv/wk for uncontrolled spaces
 - 100 μ Sv/wk for controlled spaces

To reduce radiation exposure:



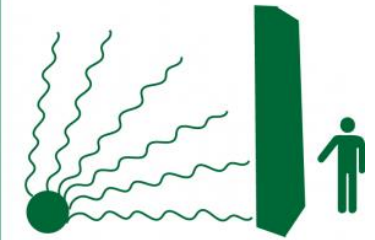
Limit Time

(Free!)



Increase Distance

(Depends)

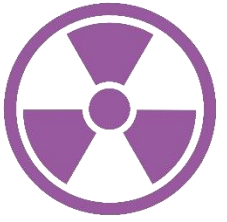


Use Shielding

(Expensive)



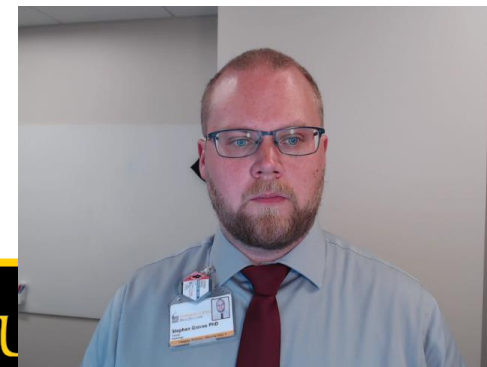
Examples



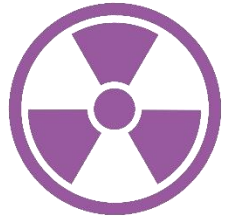
- 1.5 – 7.0 GBq of [^{131}I]NaI commonly used for thyroid cancer patients
- Exposure rate constant for ^{131}I = $59 \mu\text{Sv m}^2 / \text{h GBq}$

- 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%

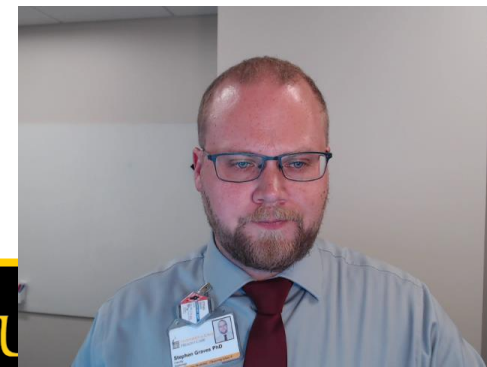
- $D = 11$ meters (~ 36 ft) would be sufficient to meet the exposure criteria



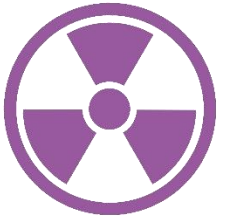
Shielding (^{131}I)



Radiation type	Most abundant emissions (>10 keV, >0.01%)	Most energetic emissions (>10 keV, >0.01%)	Shielding information (mm)
Gamma & X-ray	364.49 keV (81.2%) 636.99 keV (7.3%) 284.3 keV (6.1%)	722.91 keV (1.8%) 642.7 keV (0.22%) 636.99 keV (7.3%)	Lead: 1 st HVL = 3.9, 2 nd HVL = 3.1, 1 st TVL = 12, 2 nd TVL = 17 Steel: 1 st HVL = 32, 2 nd HVL = 14, 1 st TVL = 64, 2 nd TVL = 42 Concrete: 1 st HVL = 118, 2 nd HVL = 50, 1 st TVL = 226, 2 nd TVL = 134
Beta(-), Beta(+), electrons	606.31 keV (89.4%) 333.81 keV (7.36%) 45.62 keV (3.5%)	806.87 keV (0.40%) 629.65 keV (0.05%) 606.31 keV (89.4%)	Practical range in glass: 0.9 Practical range in plastic: 1.6



Examples



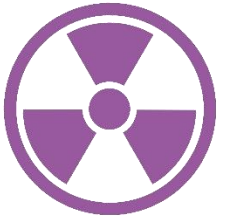
- 1.5 – 7.0 GBq of [¹³¹I]NaI commonly used for thyroid cancer patients
- Exposure rate constant for ¹³¹I = 59 μSv m² / h GBq

- Calculation parameters:
 - Goal: 20 μSv/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)



- $7.6 \mu\text{Sv m}^2 / \text{h GBq}$
- $\text{TVL} = 2.1 \text{ mm Pb}$

- 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)

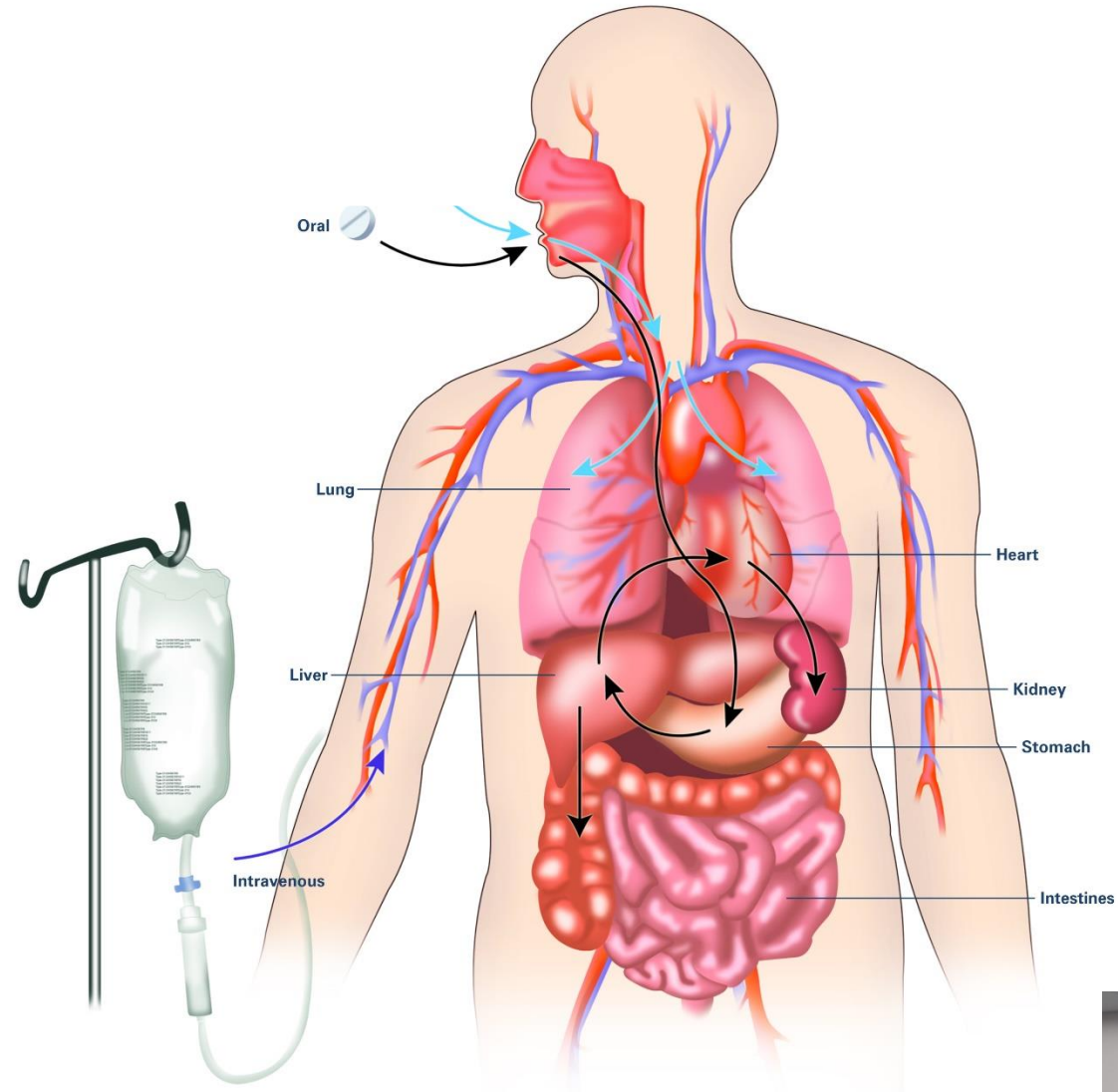
- **1.7 m (5.6 ft) sufficient to ensure $< 20 \mu\text{Sv}$ of personnel exposure.**

- 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?

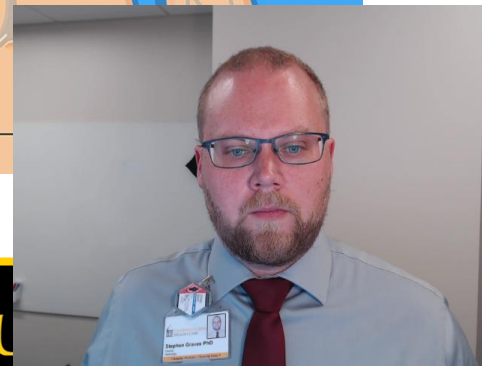
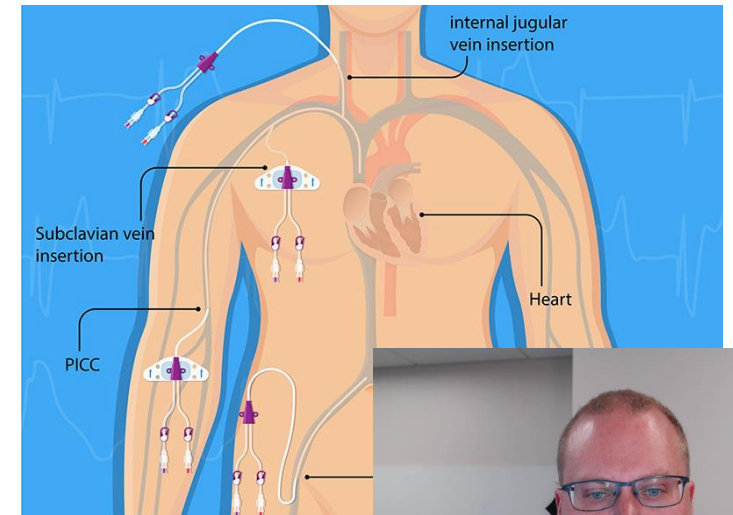
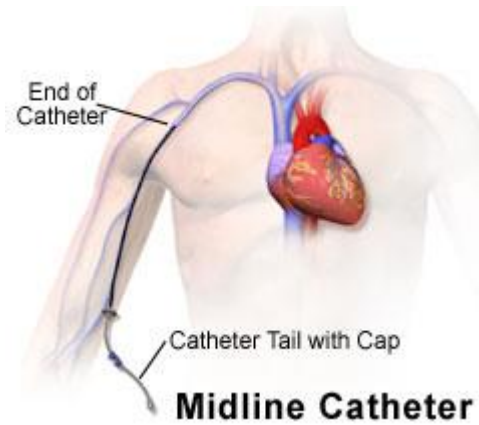
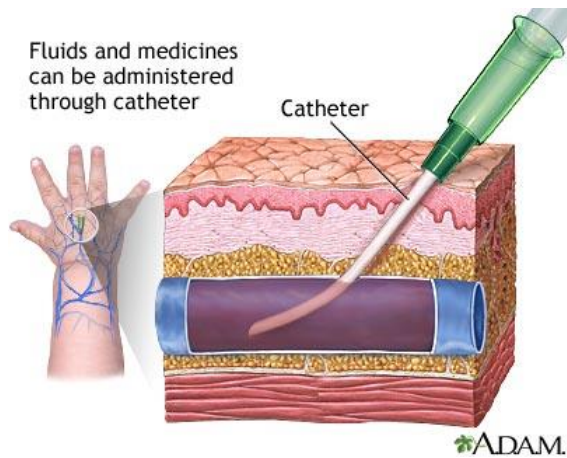
- Oral
- **Intravenous**
- Intraarterial
- Interstitial



Intravenous Administration of RPT

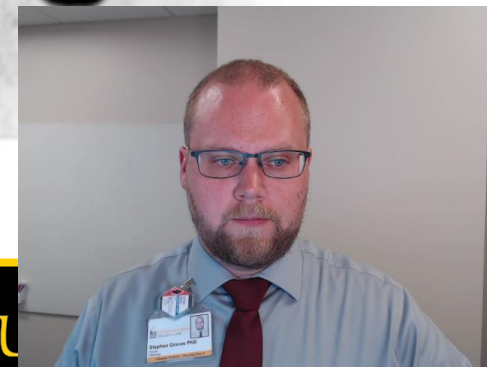
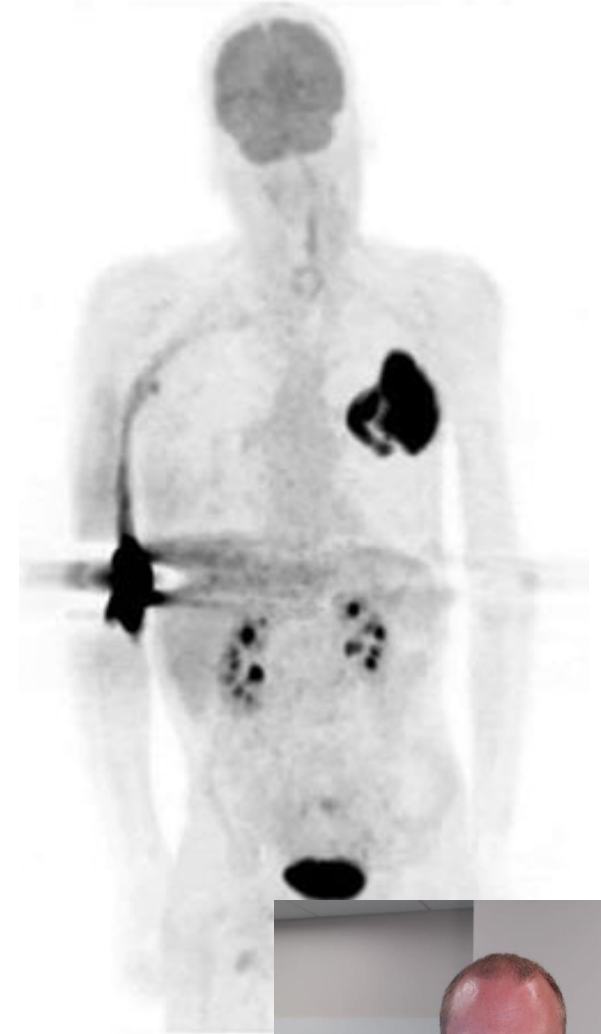
➤ Types of IV catheters

- 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 Vöö¹ · Jan Bucarius^{1,2} · Felix M. Mottaghy^{1,2}

Table 3 Summary of reported cases of therapeutic radiopharmaceutical extravasation

Reference	No. of patients with extravasation	Radiopharmaceutical	Reported extravasated activity [GBq]	Reported administered volume [ml]	Reported estimated tissue dose [Gy]	Symptoms after radiopharmaceutical extravasation ^a
Williams 2006 [52]	1	⁹⁰ Y-ibritumomab tiuxetan	0,068–0,136	60	10–20 worst case	Erythema (1d), tenderness (14d), bulla (26d), moist desquamation (29d)
Siebeneck 2008 [50]	1	⁹⁰ Y-ibritumomab tiuxetan	Not reported	Not reported	Not reported	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.
Erken 1991 [47]	3	⁹⁰ Y-colloid (radiosynovectomy)	Not reported	Not reported	Not reported	Needle track necrosis. Spontaneous healing (3m)
Terwinghe 2012 [51]	1	⁹⁰ Y-DOTATOC	3,5 (worst case)	Not reported	Not reported	Painful and swollen arm (p.i.). No symptoms arose during follow-up (no time indication).
Minsky 1987 [48]	1	³² P-sodium phosphate	0,086	76	5,02	Raised area at infusion site (p.i.).
Patton 1950 [49]	1	⁹⁰ Y-hydroxy citrate complex	Not reported	0,2	1000	Ulceration, 2cm in diameter.
Bonta 2011 [46]	1	¹³¹ I-metaiodobenzylguanidine	11,1 (worst case)	60	20–40	Forearm swelling (7d). Rash at injection site, 10x5cm (4w). Lesion still “angry looking” (7w), lesion appearance evolved to dry and scaly after corticosteroid cream.
Kawabe 2013 [53]	1	⁸⁹ Sr-Strontium chloride	0.00296	30	1.78	Slight burning pain, slight reddening and small circular swelling. No symptoms reported during follow up.

^a 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



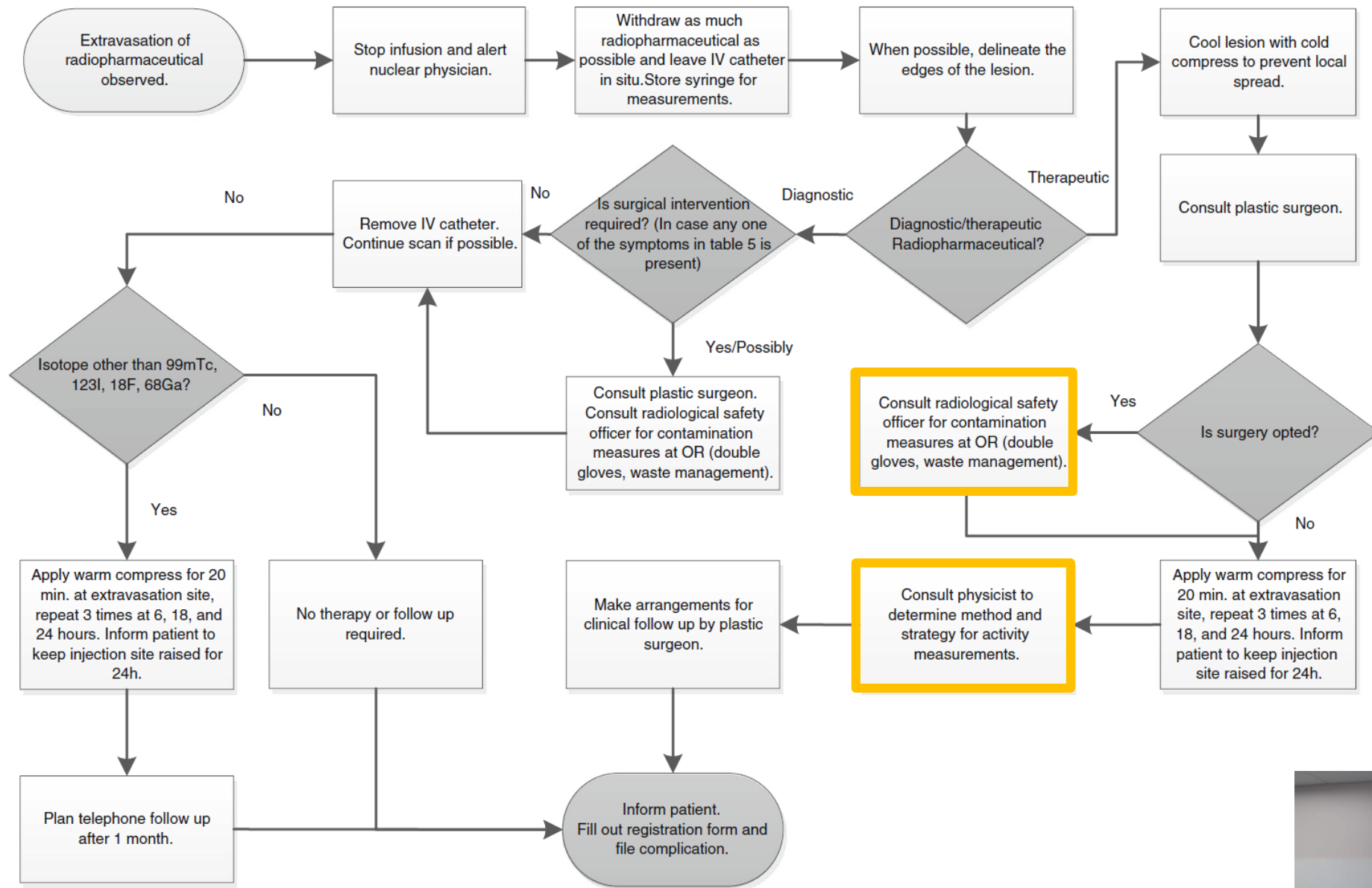
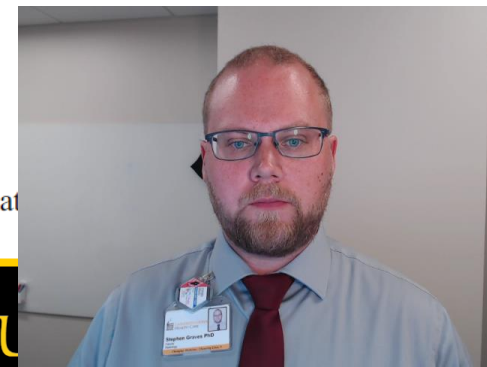
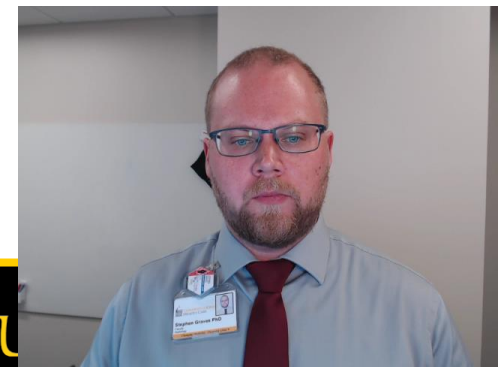


Fig. 1 Flowchart describing the protocol in use in Maastricht University Medical Center for management of radiopharmaceutical extravasation



Imaging for Fixed Activity RPT Administration

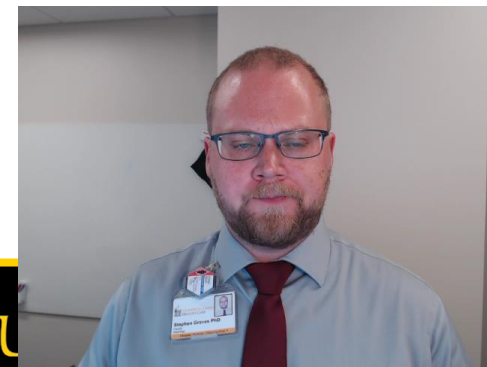
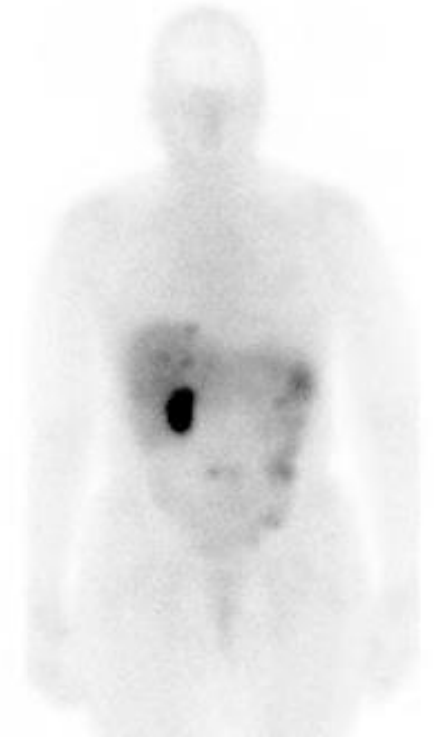


Imaging for Fixed Activity-based Administration of RPTs: **Why?**

➤ Safety!

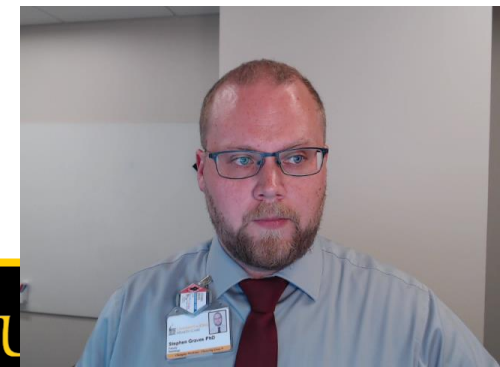
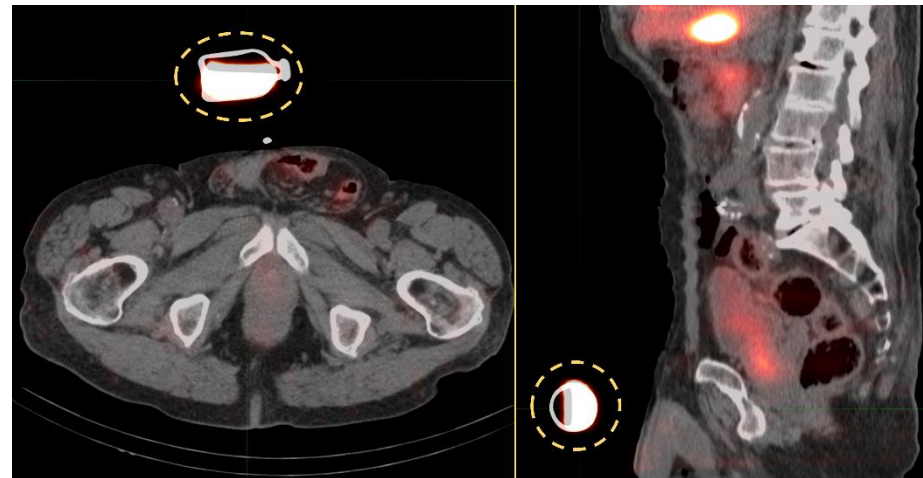


- Post-treatment imaging is always performed following ^{90}Y microsphere administration to confirm hepatic localization
- Detection of extravasation for IV-administered RPTs
- Normal organ dosimetry
 - Required for pre-treatment ^{131}I -MIBG planning
 - Recommended for post-treatment ^{177}Lu -DOTATATE safety analysis

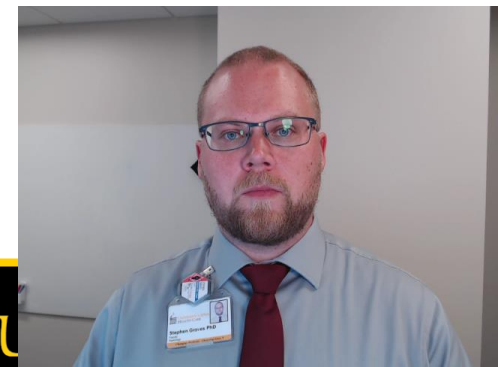


Imaging for Fixed Activity-based Administration of RPTs: **How?**

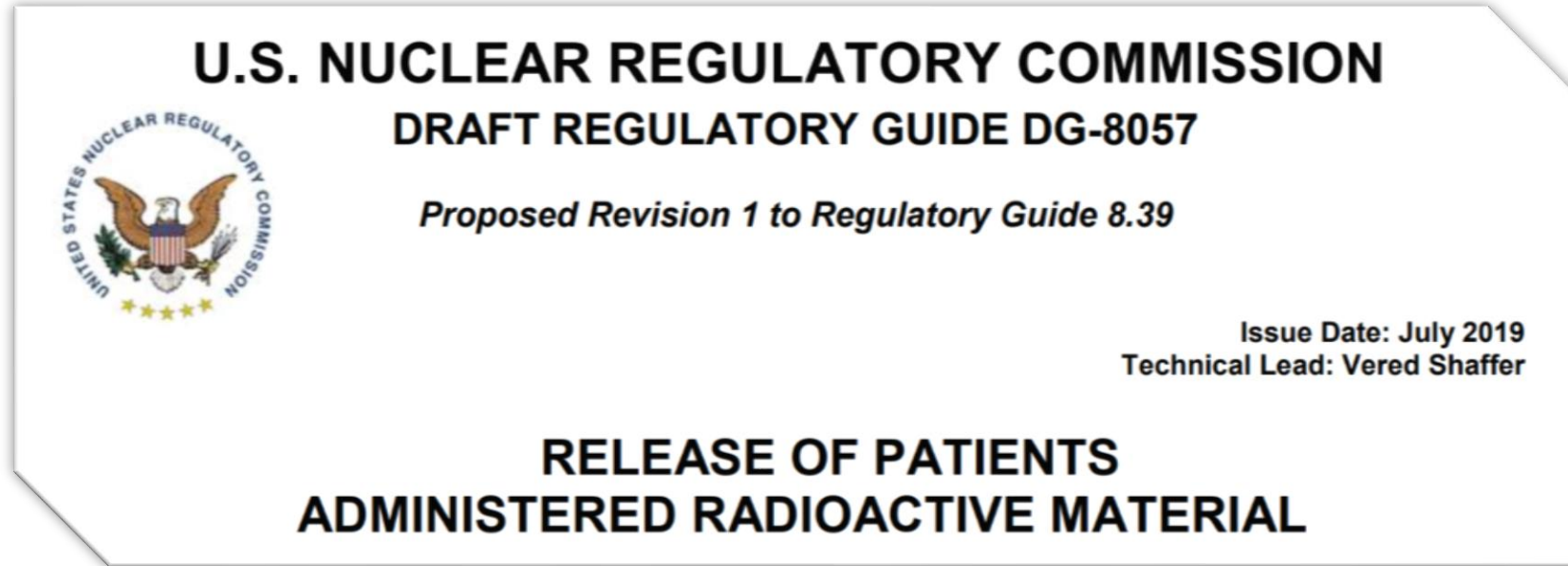
- Routine quality assurance of gamma cameras – TG177 and accrediting bodies
- Collimator and energy-window selection should be appropriate for the radioisotope
- Recommendations for quantitative SPECT imaging: MIRD 23, 24, 26
- Planar vs. SPECT/CT
 - Patient's performance status
 - Quantitative accuracy



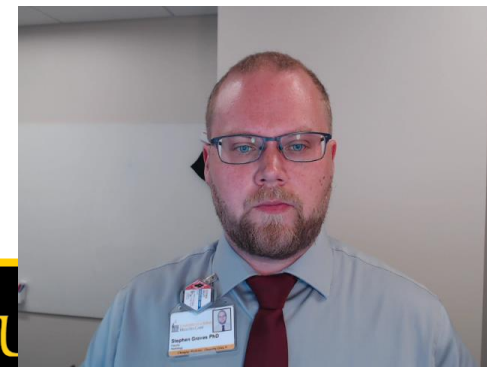
Release Criteria



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

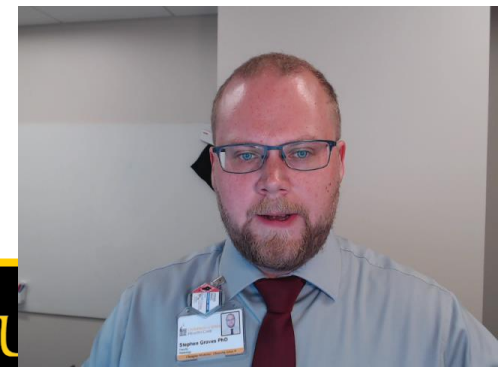


When can you release a patient? (Details)

- 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.

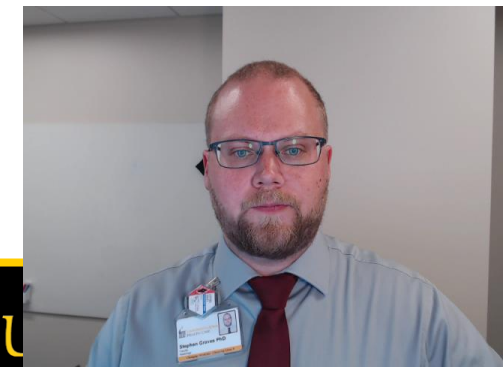
The licensee should instruct family members and caregivers to notify the treating medical facility of a medical emergency or if a patient passes away. The licensee should again tell the patient how to clean up an area contaminated with body fluids (e.g., urine, vomit).



Release criteria: Administered activity or Exposure Rate

Table 1. Activities and Dose Rates for Authorizing Patient Release^a

RADIOISOTOPE	COLUMN 1 ACTIVITY AT OR BELOW WHICH PATIENTS MAY BE RELEASED		COLUMN 2 DOSE RATE AT 1 METER, AT OR BELOW WHICH PATIENTS MAY BE RELEASED ^b	
	(GBq)	(mCi)	(mSv/h)	(mrem/h)
Ag-111	19	520	0.08	8
Au-198	3.5	93	0.21	21
Cr-51	4.8	130	0.02	2
Cu-64	8.4	230	0.27	27
Cu-67	14	390	0.22	22
Ga-67	8.7	240	0.18	18
I-123	6.0	160	0.26	26
I-125	0.25	7	0.01	1
I-125 implant	0.33	9	0.01	1
I-131	1.2	33	0.07	7
In-111	2.4	64	0.2	20
Ir-192 implant	0.074	2	0.008	0.8
P-32	(c)	(c)	(c)	(c)
Pd-103 implant	1.5	40	0.03	3
Re-186	28	770	0.15	15
Re-188	29	790	0.20	20
Sc-47	11	310	0.17	17
Se-75	0.089	2	0.005	0.5
Sm-153	26	700	0.3	30
Sn-117m	1.1	29	0.04	4
Sr-89	(c)	(c)	(c)	(c)
Tc-99m	28	760	0.58	58
Tl-201	16	430	0.19	19
Y-90	(c)	(c)	(c)	(c)
Yb-169	0.37	10	0.02	2



Release criteria: Patient-specific calculation

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:

$$D(t) = \frac{34.6 \Gamma Q_0 T_p E (1 - e^{-0.693t/T_p})}{r^2}, \quad (\text{Equation B-1})$$

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)

Γ = exposure rate constant for a point source, R/mCi \times hr at 1 centimeter (cm)

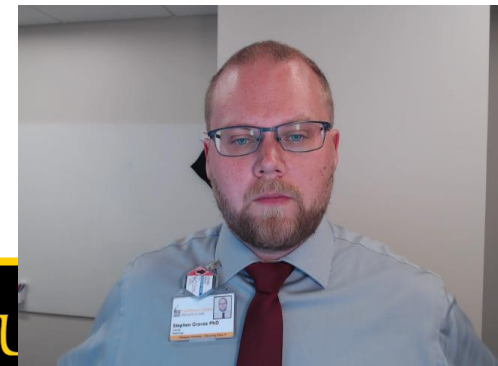
Q_0 = initial activity at the start of the time interval

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

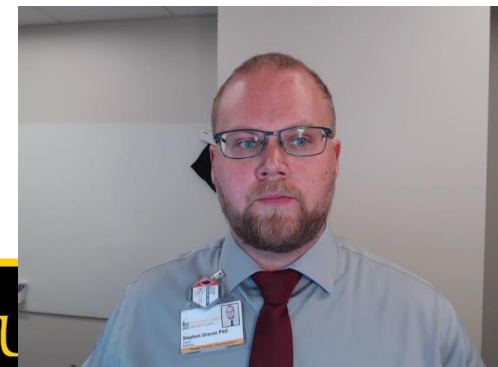
r = distance in centimeters (this value is typically 100 cm)

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

