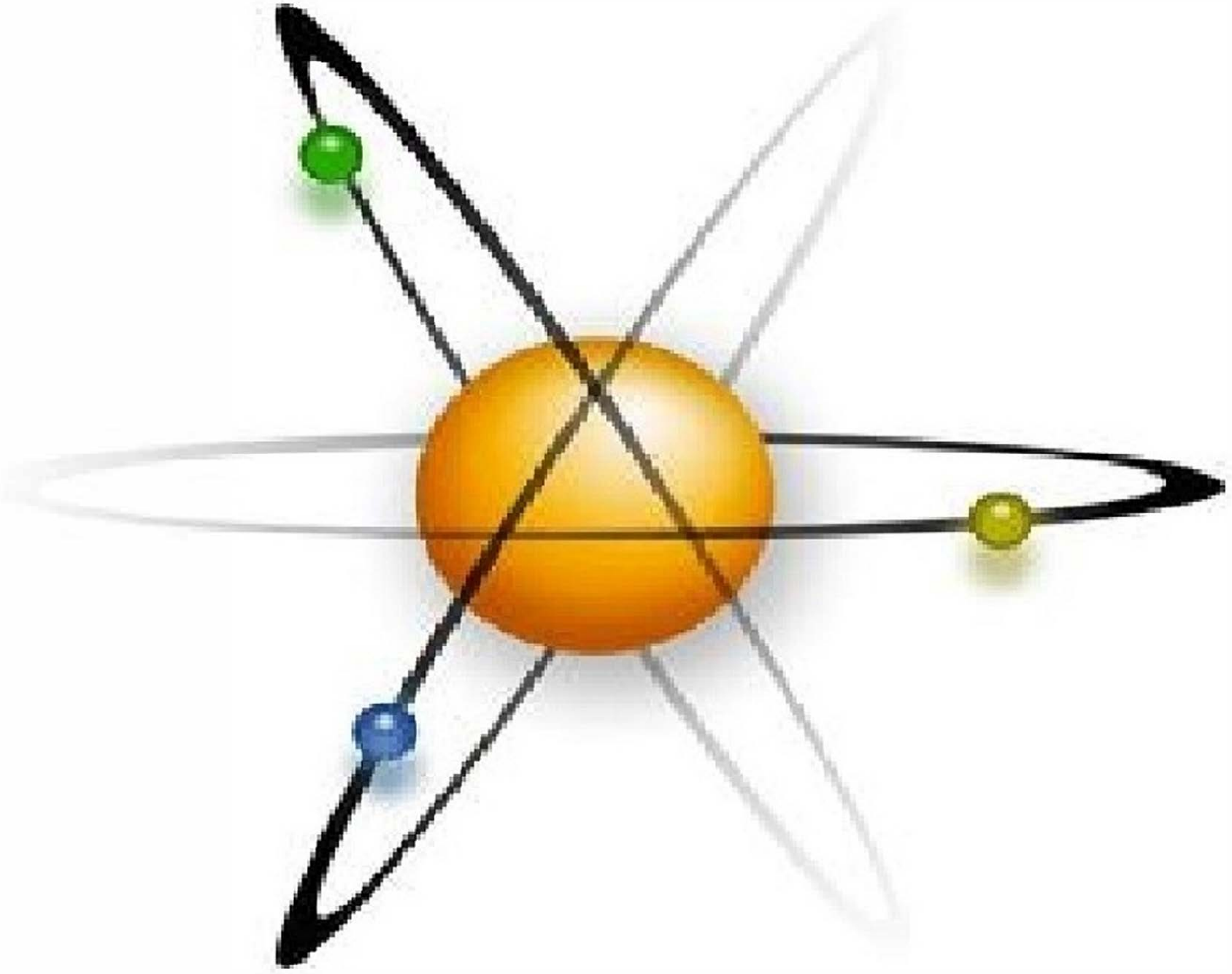

Advisory Committee on the Medical Uses of Isotopes

March 16, 2021

MEETING AGENDA
ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES
March 16, 2021
Virtual Meeting

NOTE: Sessions of the meeting may be closed pursuant to 5 U.S.C. 552(b) to discuss organizational and personnel matters that relate solely to internal personnel rules and practices of the ACMUI; information the release of which would constitute a clearly unwarranted invasion of personal privacy; information the premature disclosure of which would be likely to significantly frustrate implementation of a proposed agency action; and disclosure of information which would risk circumvention of an agency regulation or statute.

TUESDAY, MARCH 16, 2021
OPEN SESSION

	1. Opening Remarks Mr. Einberg will formally open the meeting and Mr. Williams will provide opening remarks.	**C. Einberg, NRC** **K. Williams, NRC**
	2. Old Business Ms. Jamerson will review past ACMUI recommendations and provide NRC responses.	**K. Jamerson, NRC**
10:00 – 12:30	**3. Extravasations in Nuclear Medicine** Dr. Jochem van der Pol will provide an overview of his study on the consequences of radiopharmaceutical extravasation and therapeutic interventions.	**J. van der Pol, MD, Maastricht University Medical Centre**
	4. Open Forum The ACMUI will identify medical topics of interest for further discussion.	**ACMUI**
	5. Patient Release Evaluation of Emerging Brachytherapy Sources Dr. Tapp will provide an overview of the current status of the NRC's evaluation of patient release following administration of new emerging brachytherapy sources.	**K. Tapp, PhD, NRC**
12:30 – 1:00	**BREAK**	
	6. ACMUI Reporting Structure Ms. Jamerson will provide an overview of the current reporting structure. Members will discuss the reporting structure of the Committee and provide feedback to the NRC.	**K. Jamerson, NRC**
1:00 – 3:00	**7. Calibration Procedures for Brachytherapy Sources** Dr. Larry DeWerd will provide a presentation on the calibration procedures for existing brachytherapy sources and considerations for emerging manual brachytherapy sources.	**L. DeWerd, PhD, University of Wisconsin**
	8. Open Forum The ACMUI will continue discussion on medical topics of interest.	**ACMUI**

9. Administrative Closing **K. Jamerson, NRC**

Ms. Jamerson will provide a meeting summary and propose dates for the fall 2021 meeting.

3:00	**ADJOURN**

	ITEM	DATE	STATUS		Target Completion Date for NRC Action
17	The ACMUI endorsed the Appropriateness of Medical Event Reporting Subcommittee report and the recommendations provided therein.	9/10/2019	*Partially Accepted*	Open	Summer/Fall 2021
18	The ACMUI endorsed the Evaluation of Extravasations Subcommittee Report, as amended, to note that under future revisions to Part 35 rulemakings, extravasations be captured as a type of passive patient intervention in the definition of patient intervention.	9/10/2019	*Accepted*	Open	Summer/Fall 2021

	ITEM	DATE	STATUS		Target Completion Date for NRC Action
4	The ACMUI endorsed the Patient Intervention subcommittee report, as presented, and the recommendations provided therein.	03/30/2020	*Accepted*	Open	Summer/Fall 2021
10	The ACMUI endorsed the Medical Event Subcommittee Report as presented.	09/21/2020	*Accepted*	Propose closure	
11	As part of the Non-Medical Events report, the ACMUI recommended to the NRC staff and/or NMP to evaluate the issue of detection of short-lived medical isotopes in municipal waste (waste from nuclear medicine patients that might be triggering the landfill alarms) and provide some level of guidance, best practices, or additional instructions.	09/21/2020	*Accepted*	Open	Fall 2021
12	The ACMUI tentatively scheduled its spring 2021 meeting for March 15-16, 2021. The alternate date is March 22-23, 2021. Virtual or in-person meeting is TBD, as well as timing of next ACMUI Commission meeting.	09/22/2020	*Accepted*	Propose closure	

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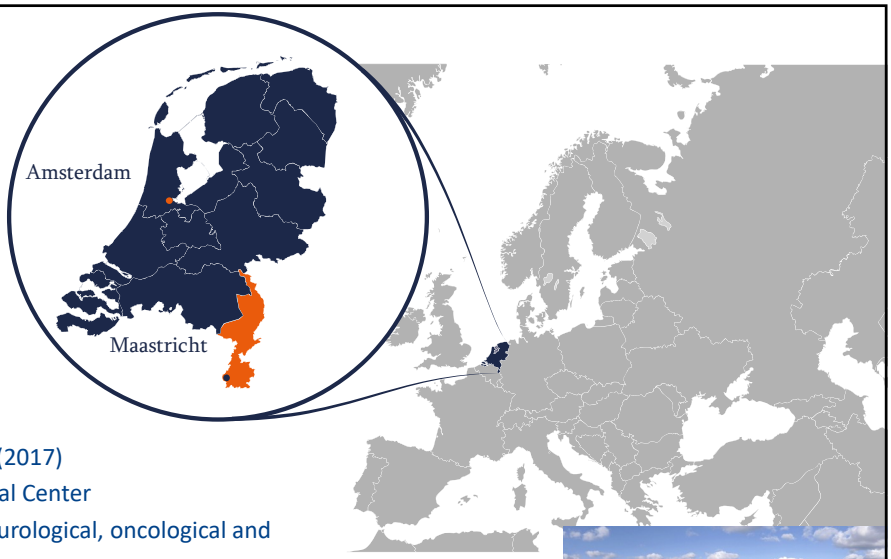
Radionuclide Extravasation

March 16, 2021

Jochem van der Pol
Nuclear Medicine Physician
Maastricht University Medical Center

Introduction



- Jochem van der Pol
- Nuclear Medicine Physician (2017)
- Maastricht University Medical Center
- Clinical area's of interest: neurological, oncological and cardiovascular imaging
- Scientific area's of interest: cardiovascular nuclear imaging

Extravasation Literature Study

- Discussion following a case of 99mTc-tracer extravasation
- Protocol: how to act in case of extravasation
- No guidelines Dutch Association of Nuclear Medicine (NVNG), EANM, SNMMI, DGN (Germany)
- → find literature

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Extravasation Literature Study

- Local protocol: how to act in case of extravasation?
- No guidelines Dutch Association of Nuclear Medicine (NVNG), EANM, SNMMI, DGN (Germany)
- → extensive literature search and analysis, why not publish…

Eur J Nucl Med Mol Imaging (2017) 44:1234–1243
DOI 10.1007/s00259-017-3675-7

REVIEW ARTICLE

Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review

Jochem van der Pol[1] · Stefan Vöö[1] · Jan Bucerius[1,2] · Felix M. Mottaghy[1,2]

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Extravasation Literature Study

- Local protocol: how to act in case of extravasation?
  - Can extravasation cause deterministic effects, such as skin burn?
  - Should you apply any kind of therapy?
  - Cooling or warming?
  - Should you perform dosimetry and how?
  - ….

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Methods

- Extensive literature search in Pubmed and Embase
- Search strings:

Table 1 Search strings applied in PubMed/MEDLINE and Embase with search results specified to search engine and search strings

No.	Search strings[a]	Pubmed/MEDLINE	Embase
1	"Extravasation of Diagnostic and Therapeutic Materials" [Mesh] OR "Extravasation of Diagnostic and Therapeutic Materials" OR "extravasation" OR "infiltration" OR "misadministration"	110.807	171.853
2	"I-123" OR "I-124" OR "I-125" OR "I-131" OR "Tc-99m" OR "F18" OR "Ga-68" OR "In-111" OR "Tl-201" OR "Rb-82" OR "N-13" OR "O-15" OR "C-11" OR "Er-169" OR "Re-186" OR "Sr89" OR "Sm-153" OR "Y-90" OR "Ra-223" OR "P-32" OR Lu177	213.922	361.049
3	"Radiopharmaceuticals"[Mesh] OR "Radiopharmaceuticals" OR "Radioisotopes"[Mesh] OR "Radioisotopes"	301.588	15.949
4	1 AND (2 OR 3)	2.153	3.493

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Methods

- Merging of results Embase and Pubmed
- Screening of abstracts by two persons
- If abstract mentioned humane radioactive tracer extravasation, publication was marked for further analysis.
- Marked publications were retrieved from online sources, university libraries or by tracking authors and subsequent email correspondence
- Bibliographies were screened to complement database search

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Methods

- Data was extracted from publications:
  - Number of cases
  - tracer involved
  - Injection place
  - Estimated extravasated volume and activity
  - Estimated tissue dose
  - Follow up duration and method
  - Applied medical interventions
  - Advised/discouraged

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Results

- 4523 abstracts (1123 in both search engines)
  - Rejected abstracts
    - 1012 animal studies
    - 2622 extravasation/infiltration of substance other than radiopharmaceutical
    - 196 Extravasation as a pathological finding not associated with injection of radiopharmaceutical (ie 99mTc-MAG3 excretion
    - 603 Radionuclide use for other purposes (s.a. radio-immunoassays)

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Results

- Full text retrieval 81 publications
  - After screening references, a further 27 publications were retrieved (108)
- 44 publications about radiopharmaceutical extravasation:
  - 37 diagnostic
  - 8 therapeutic
  - 10 expert opinion based publications

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Results: Diagnostic Tracer Extravasations

Table 2 Summary of reported cases of diagnostic radiopharmaceutical extravasation

References	Total reported cases	Radiopharmaceutical	No. of patients with reported radiation injury	No. of patients with reported follow-up	Most severe injury reported
[8–17]	332	18F-FDG	0	0	
[18–31]	2584	^{99m}Tc bone tracers	0	0	
[32]	3	^{99m}Tc-MAA	0	0	
[33]	1	^{99m}Tc-DMSA	0	0	
[34, 35]	10	^{99m}Tc-DTPA	0	0	
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[37]	1	^{99m}Tc-MAG3	0	0	
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[19]	38	^{99m}Tc-sulfurcolloid	0	0	
[19]	16	^{99m}Tc-microspheres	0	0	
[42]	1	^{131}I-iodocholesterol	1	1	Erythematous plaque and pruritus.
[43–45]	12	^{201}Tl-thallous chloride	2	2	Radiation ulcer
Total	3016		3	3	

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Results: Diagnostic Tra

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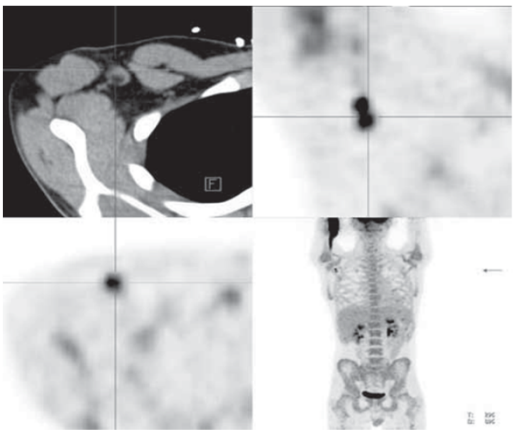
Total	3016	



Wagner, T., et al. (2011). "A false-positive finding in therapeutic evaluation: hypermetabolic axillary lymph node in a lymphoma patient following FDG extravasation." Nucl Med Rev Cent East Eur **14**(2): 109-111.

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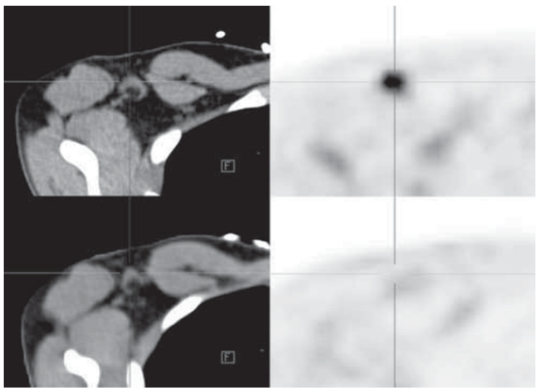

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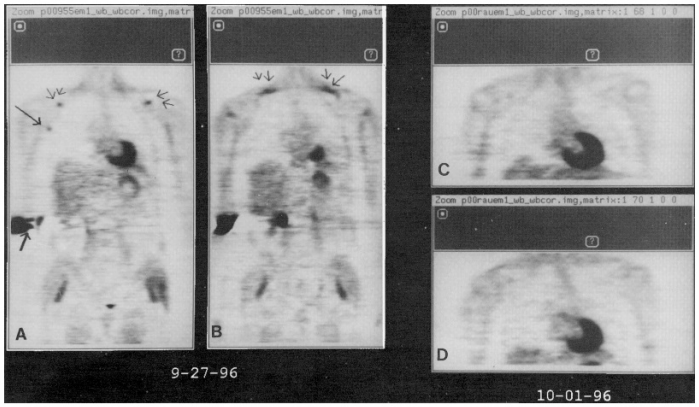

Alibazoglu, H., et al. (1998). "Injection artifact on FDG PET imaging." Clinical Nuclear Medicine **23**(4): 264-265.

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Results: Diagnostic Tracer Extravasations

Table 2 Summary of reported cases of diagnostic radiopharmaceutical extravasation

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Total	3016		3	3	

- Evaluation 190 FDG PET scans
- 39 (21%) with visible focus injection site
- 36 less than 1% injected dose
- 3 with 3,0%, 7,7% 17,5%
- Percent change in SUV max ranged from 0-21%

Hall N., Z. J. (2006). "Impact of FDG extravasation on SUV measurements." J Nucl Med **47**(suppl 1): 115P. (SNMMI 2006 Poster presentation)

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Results: Diagnostic Tra

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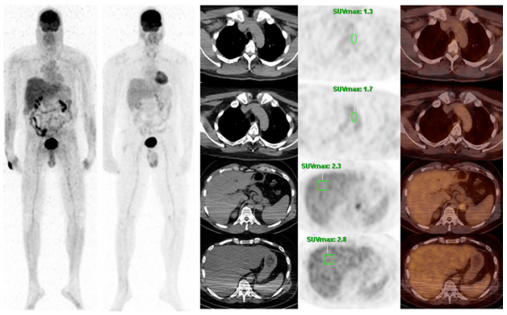
Total	3016	

- Evaluation 400 FDG PET scans
- 42 (10,5%) with noticable extravasation
- 5 cases with repeat studies without therapy
- Mediastinal SUV change 9,3%
- Hepatic SUV change: 11,7%



Osman, M. M., et al. (2011). "FDG Dose Extravasations in PET/CT: Frequency and Impact on SUV Measurements." Front Oncol **1**: 41.

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Results: Diagnostic Tracer Extravasations

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Results: Diagnostic Tra

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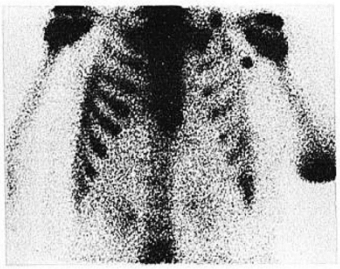

Fig. 1. Tc-99m IDP bone imaging in a 58-year-old woman following right mastectomy for carcinoma. The partially interstitial injection in the left antecubital fossa is partially shielded by a lead sheet. What appears to be uptake in a single node in the left axilla is seen.

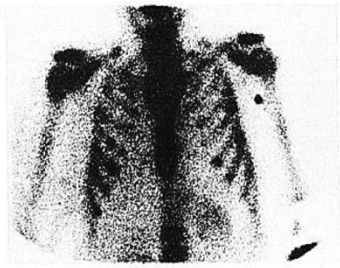

Fig. 2. Tc-99m IDP bone imaging in a 65-year-old woman. A left mastectomy has been performed for carcinoma. There is a lead sheet over the partially interstitial injection in the left antecubital fossa. What appears to be uptake in a single lymph node adjacent to the proximal femoral shaft is seen.

Boxen, I. (1985). "Inadvertent lymphoscintigraphy?" Clin Nucl Med 10(1): 25-26

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Results: Diagnostic Tracer Extravasations

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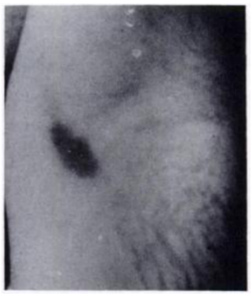

FIGURE 1
Radiation burn evident by inspection 20 days after injection.

- 34Mbq-Iodocholesterol
- After 13 days erythematous pruritic patch
- Complete tracer retention after 7 days

Breen, S. L. and A. A. Driedger (1991). "Radiation injury from interstitial injection of iodine-131-iodocholesterol." J Nucl Med **32**(5): 892.

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Results: Diagnostic Tracer Extravasations

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[43–45]	12	^{201}Tl-thallo
Total	3016	

A recent report described radiation damage to the skin and subcutaneous tissue of a patient in whom part of 2 mCi (74 MBq) Thallium-201 injection to be given intravenously was inadvertently injected subcutaneously. It was estimated that the maximum dose the patient could have received at the injection site was 20000 rad (200 Gy). Two years after the injection the patient was referred to the hospital with ulceration at the injection site probably due to radiation damage. Skin grafting was performed.

Anon. (1988). "European system for reporting of adverse reactions and drug defects: Third report 1984-1985." European Nuclear Medicine Society News Letter(9): 487-490.

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Results: Therapeutic Tracer Extravasations

Table 2 Summary of reported cases of diagnostic radiop

References	Total reported cases	Radiopharm
[8–17]	332	18F-FDG
[18–31]	2584	^{99m}Tc bone t
[32]	3	^{99m}Tc-MAA
[33]	1	^{99m}Tc-DMS
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Results: Therapeutic Tracer Extravasations

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

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Results: Therapeutic Tracer Extravasations

Table 3 Summary of reported cases of therapeutic radiopharmaceutical extravasation

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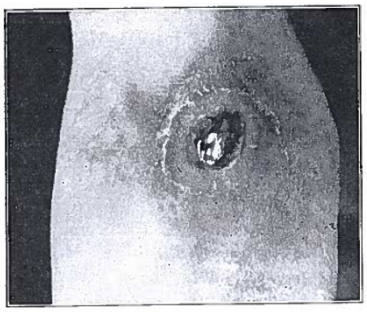

Fig. 1.—Ulcerated area eight weeks after injection of radioactive yttrium chloride.

Anon. (1988). "European system for reporting of adverse reactions and drug defects: Third report 1984-1985." European Nuclear Medicine Society News Letter(9): 487-490.

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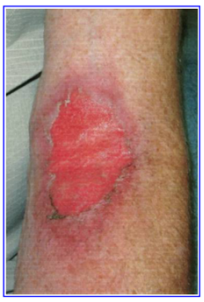

Figure 1. Image of the patient's antecubital fossa, showing wet desquamation at day 29.

Anon. (1988). "European system for reporting of adverse reactions and drug defects: Third report 1984-1985." European Nuclear Medicine Society News Letter(9): 487-490.

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Conclusions: Literature Study

- Extravasation of tracers is common
- No adverse effects of 18F, 99mTc, 123I and Ga68 reported -> no reason to assume extravastion of these tracers has clinical significance.
- Sporadic reports of other diagnostic tracers have described soft tissue lesion
- Multipele reports of severe adverse events following therapeutic tracer extravasation.

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What is the frequency of extravasations in Nuclear Medicine and what criteria should be used for identifying an extravasation (visualization, % injected dose, etc.)?

- Frequency: unknown
  - MUMC 2007-2018
    - Reported radionuclide extravasations 3 (FDG) (est. 6.000/year)
    - Reported contrast extravasation: 91 (est. 50.000/year)
  - Literature
  - No national registration

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What is the frequency of extravasations in Nuclear Medicine and what criteria should be used for identifying an extravasation (visualization, % injected dose, etc.)?

- What criteria:
  - Clinical: painful injection, swelling and redness or palor
  - %Injected dose
    - Diagnostic: doesn't seem to be relevant.
      - Quality is a parameter any nuclear medicine physician should monitor.
      - If quality is below standards, consider repeat study, always perform internal registration for quality improvement (irrespective of the cause)
    - Therapeutic: any extravasation noted at any timepoint should be adequately treated and registered, irrespective of dose

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What is the appropriateness of reporting extravasations that result in a certain tissue dose threshold (0.5 Sv) as a Medical Event (Adverse Event)?

- How will the dose be calculated?
- Erythema threshold 2.5Sv

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How does the European community address reporting of extravasations?

- No European legislation

> *"The EU does not define health policies, nor the organisation and provision of health services and medical care. Instead, its action serves to complement national policies and to support cooperation between member countries in the field of public health."*

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How does the European community address reporting of extravasations?

- Dutch legislation:
  - No definitions or mentioning of (radiopharmaceutical) extravasation
  - Different definitions of adverse events:
    - Complications
    - Incidents
    - Calamity

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How does the European community address reporting of extravasations?

- **Complication**: *"an unintentional and undesired outcome during or following the actions of a medical care provider, which demands adaptation of the medical procedure of causes irreparable damage"*
  - Worked according to medical standards
  - Unintended oucome
- **Incident**: *""An unintentional or unexpected event, that is related to quality of healthcare and that **could have** led to the death of a client [patient] or serious harmful consequences for a client [patient]"*
- **Calamity**: *"An unintentional or unexpected event, that is related to quality of healthcare and that **has** led to the death of a client [patient] or serious harmful consequences for a client [patient]"*

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How does the European community address reporting of extravasations?

- When do we report to healthcare authorities:
  - **Calamities**
  - Incidents and complications are reported and registered locally, as advised by healthcare professional societies.
    - unless when the nature is not clear and calamity is not ruled out → Authorities advise on event.

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What are the issues/challenges in determining the tissue dose from an extravasation?

Geometry

-Point source → not realistic, distance > 10 times diameter

-Disc shaped source, complex mathematics

-Activity concentration is a great factor in dose calculations

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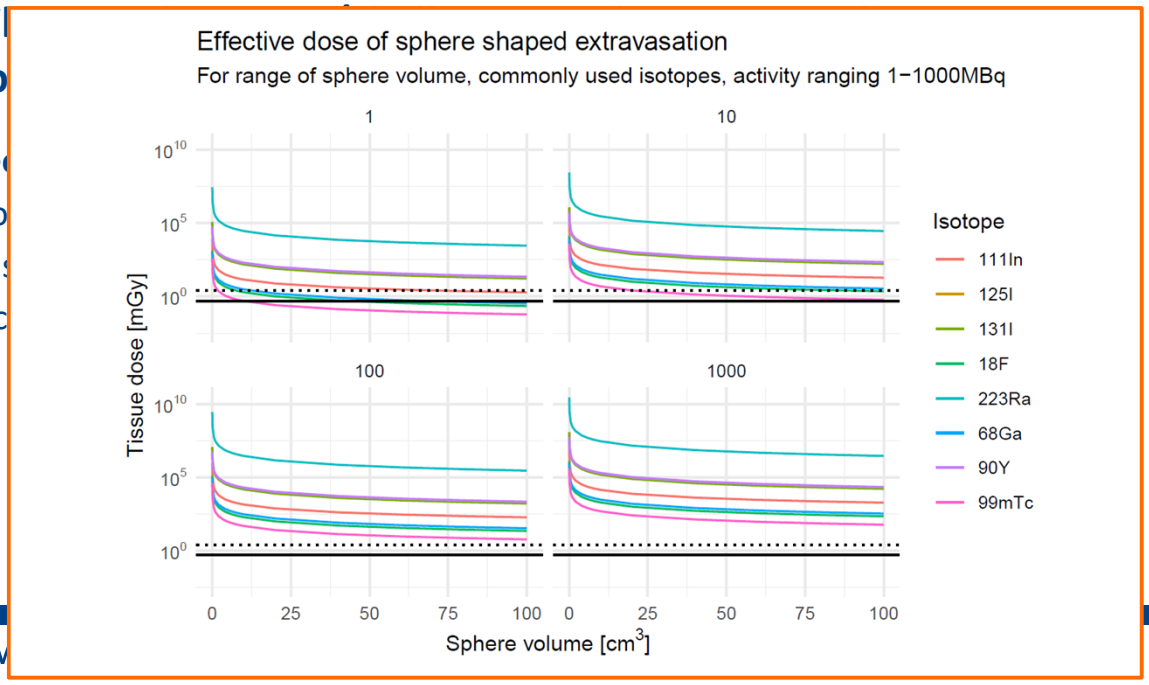

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What are the issues/challenges in determining the tissue dose from an extravasation?

Geometry

-Point source → not realistic, distance > 10 times diameter

-Disc shaped source, complex mathematics

-Activity concentration is a great factor in dose calculations

-What about cystic distribution?

-Homogenity of distribution?

-**Real world: very complex geometry with evolving boundaries**

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What are the issues/challenges in determining the tissue dose from an extravasation?

Biological half life

-Probably less relevant for short half life PET tracers

-More relevant for tracers with longer half life

-Dynamic behaviour: multiple acquisitions

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What personnel training, qualifications, and quality assurance should be in place to monitor/prevent for extravasations in medicine?

- Technician
  - Properly trained for obtaining IV access
  - (Special exception to perform medical procedure)
- Nuclear medicine physician/Radiologist
  - Always check image quality. If not adequate: repeat study!
  - Signs of (significant) tracer accumulation near injection site?

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What personnel training, qualifications, and quality assurance should be in place to monitor/prevent for extravasations in medicine?

- Radiation safety officer/quality officer
  - Keep local registration of extravasation cases
    - Goal: quality improvement
      - Train technicians/NM physicians with bad track records

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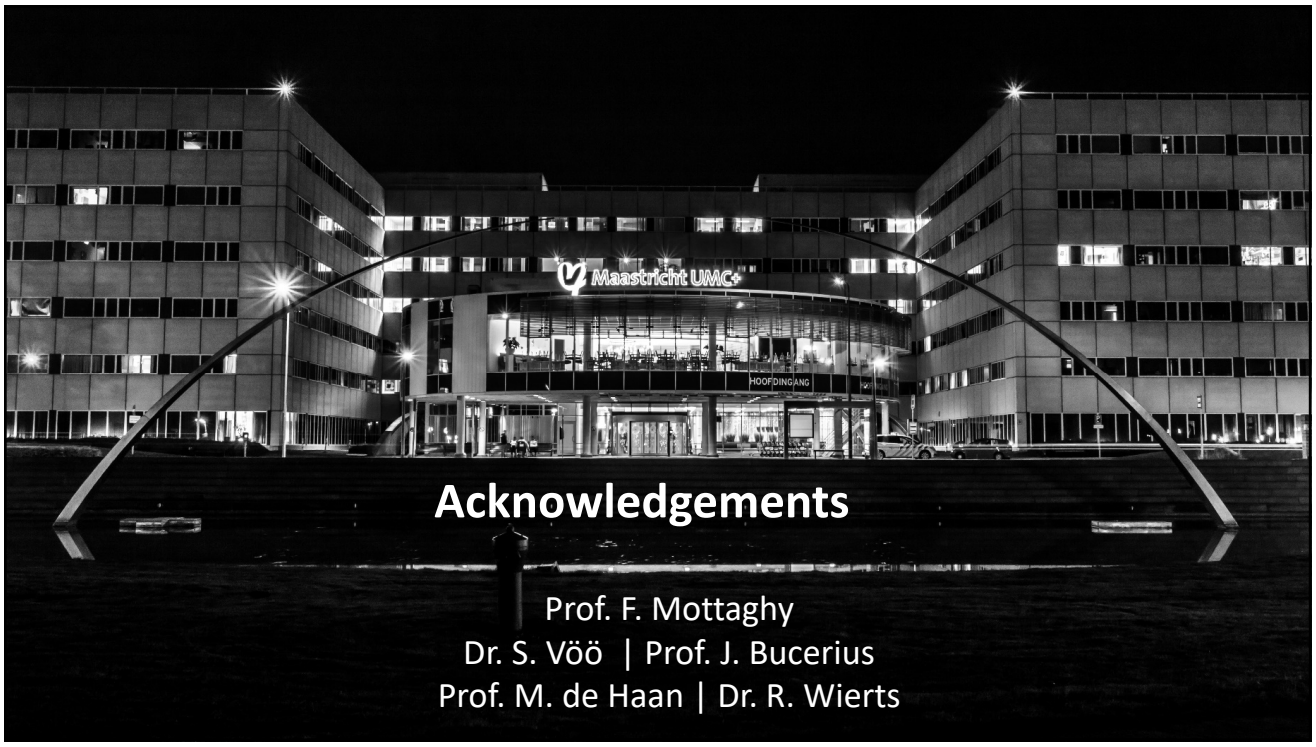

Acknowledgements

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Dr. S. Vöö | Prof. J. Bucerius
Prof. M. de Haan | Dr. R. Wierts

OPEN FORUM

No Handout

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Patient Release Considerations Associated with Temporary Brachytherapy Devices

Katie Tapp, PhD
Medical Radiation Safety Team
March 16, 2021

1

Overview

- This presentation will provide an overview of
  - Temporary implant devices,
  - The scope of staff's evaluation of patient release for those with temporary implants,
  - The many regulatory questions the staff intends to answer through its evaluation,
  - Next steps.

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Patient Release Regulations (10 CFR 35.75)

- A licensee may authorize the release from its control of any individual who has been administered implants containing byproduct material if the dose to any other individual from exposure to the released individual is not likely to exceed 5 mSv (0.5 rem).
- A licensee shall provide the released individual with instructions on actions recommended to maintain doses to other individuals as low as is reasonably achievable if the dose to any other individual is likely to exceed 1 mSv (0.1 rem).

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Patient Release Regulations (10 CFR 35.75)

- Before 2002, patient release regulations only allowed release of permanent implants
- In 2002, the regulations were amended to allow patients to be released with all types of implants if the dose limits were met.
- Regulatory Guide 8.39 does not provide guidance for temporary implants.

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Temporary Implants

- Temporary implants are expected to be removed from the patient at a specific time to deliver the prescribed dose.
- Examples of temporary implants include:
  - Eye Plaques
  - Brachytherapy Seeds
  - Emerging brachytherapy devices, including:
    - Alpha DaRT
    - CivaDerm

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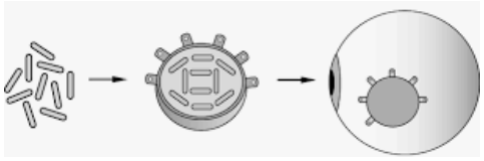
Eye Plaque Brachytherapy

- Plaques are temporarily attached to the wall of the eye
- The plaque contains brachytherapy sources and shielding on the backside
- Licensed under 10 CFR 35.400 and patients released under 10 CFR 35.75.



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Brachytherapy Seeds

- Ir-192 seeds have been used in ribbons for temporary implant brachytherapy.
- Many of these patients stay in the hospital during treatment.
- I-125 seeds are also used for radioactive seed localization. These patients are released following implantation and return to have the seeds excised.

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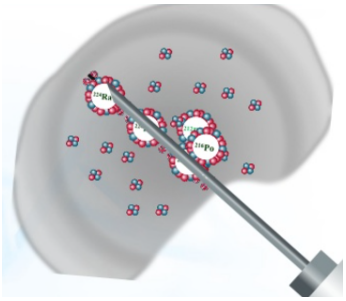
Alpha Dart

- Alpha DaRT is the first manual brachytherapy device which uses diffusing alpha-emitting radiation for therapeutic treatment.
- Alpha Dart seeds contain ^{224}Ra.
- Inside the tumor, the source diffuses as the ^{224}Ra atoms decay down its decay chain.



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Alpha Dart (cont.)

- Currently, this therapy utilizes temporary implants but they may be used for permanent therapy in the future.
- Staff expects to provide a draft 10 CFR 35.1000 licensing guidance for the ACMUI review in early summer.

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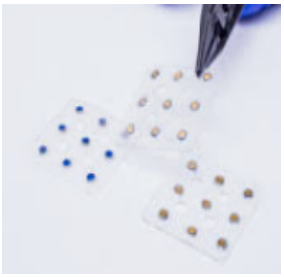
CivaDerm

- Temporary brachytherapy using Pd-103 sources affixed to the skin surface.
- Patients will need to return to the licensee to have the sources removed.
- Sources are self shielded with a cold and hot side.
- Staff is still evaluating the licensing pathway for use.



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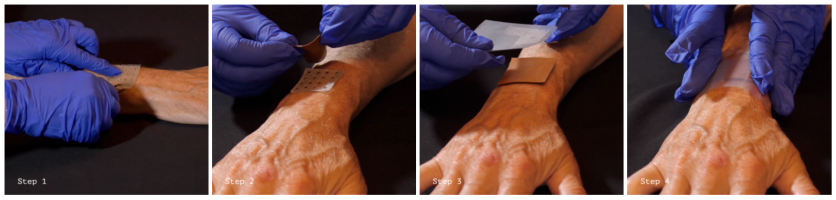
CivaDerm (cont.)

- Sources are affixed by:
  - placing on clean, dry skin
  - Attached with a surgical bandage
  - Secured with additional radiation shield cover
  - Covered with a waterproof shield



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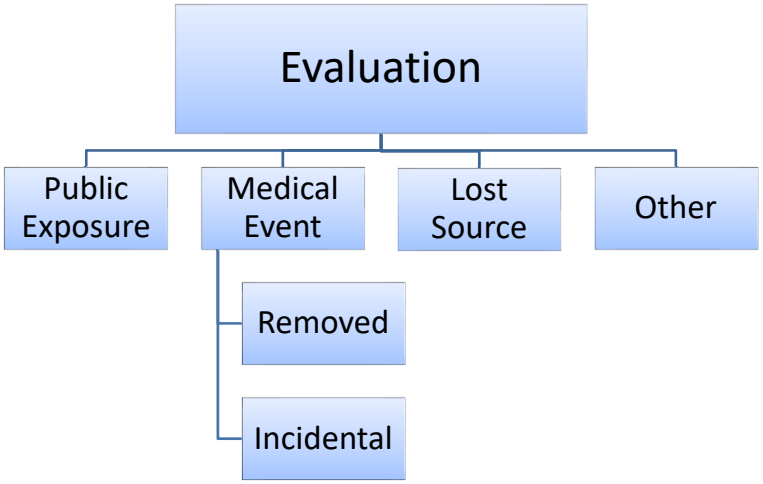
Regulatory Considerations



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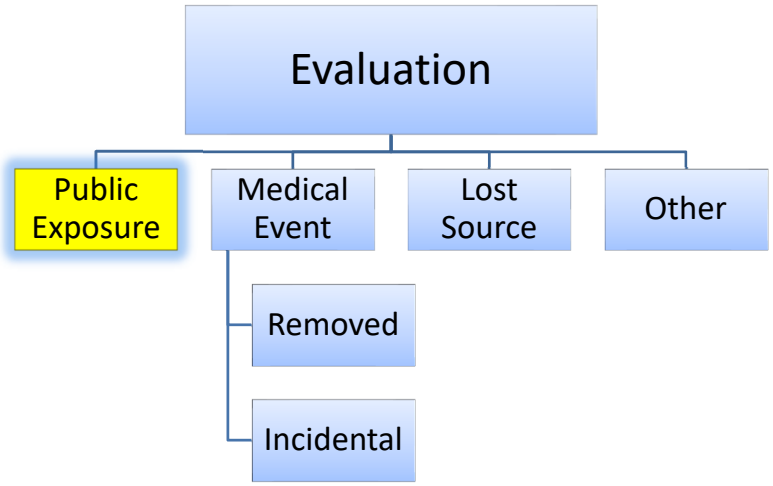
Regulatory Considerations



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Patient Release

- 10 CFR 35.75 states licensees may authorize the release from its control of **any individual** who has been administered implants containing byproduct material if the dose to any other individual from exposure to the released individual is not likely to exceed 5 mSv (0.5 rem).
- Licensees will need confidence that the source will not become dislodged, as it is possible a loose source could exceed this limit.

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Public Dose Limits

- Public dose limits in Part 20 exclude exposure to **individuals** administered radioactive material and released under 10 CFR 35.75.
- Public dose limits do not appear to exclude dose from sources which are dislodged from patients.
- Further evaluation is on-going to determine if public dose limits listed in Part 20 apply to sources dislodged from patients.

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Public Exposure Potential

- Licensing evaluations prior to authorizing release of patients with temporary implants must consider:
  - Ease of which a source could become dislodged, and
  - Public exposure potential

Dose rate for maximum activity sheet for CivaDerm		
	Dose rate at 5 cm (mrem/hr)	Dose rate at 100 cm (mrem/hr)
Cold	968	2.52
Hot	23,883	31.23

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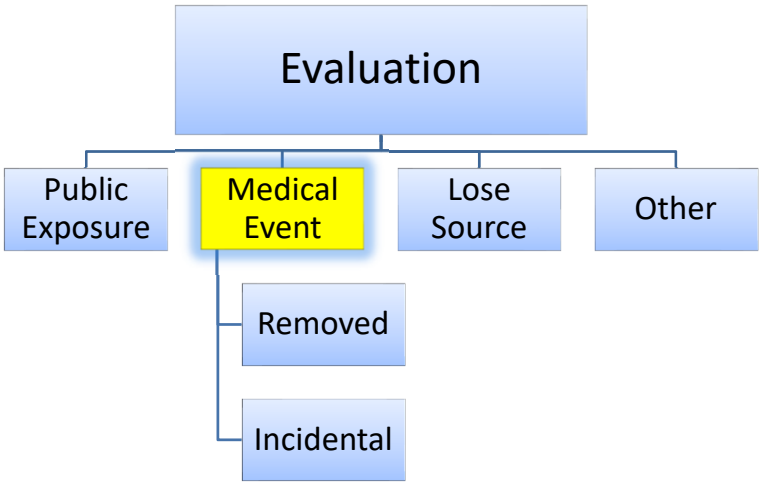
Regulatory Considerations



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Licensee Evaluation

- 10 CFR 35.41 requires licensees to have procedures to ensure high confidence that each administration is in accordance with the written directive.
- These procedures must address the following items:
  - Verifying the administration is in accordance with the written directive, and
  - Determining if a medical event has occurred.

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Medical Event

- If a source is dislodged or if a patient does not return at a specified time, it could lead to a medical event under 10 CFR 35.3045:
  - (a.1.i) a dose that differs from the prescribed dose by more than 0.5 Sv (50 rem) to an organ or tissue and the total dose delivered differs from the prescribed dose by 20 percent or more, or

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Medical Event (cont.)

- (a.1.iii) A dose to the skin or an organ or tissue other than the treatment site that exceeds by
  - (A) 0.5 Sv (50 rem) or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration; and
  - (B) 50 percent or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration.

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Patient Intervention

- Patient intervention means actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration.
- If the source comes off due to an **action** by the patient, it could be considered patient intervention and not a medical event.
- More guidance is needed.

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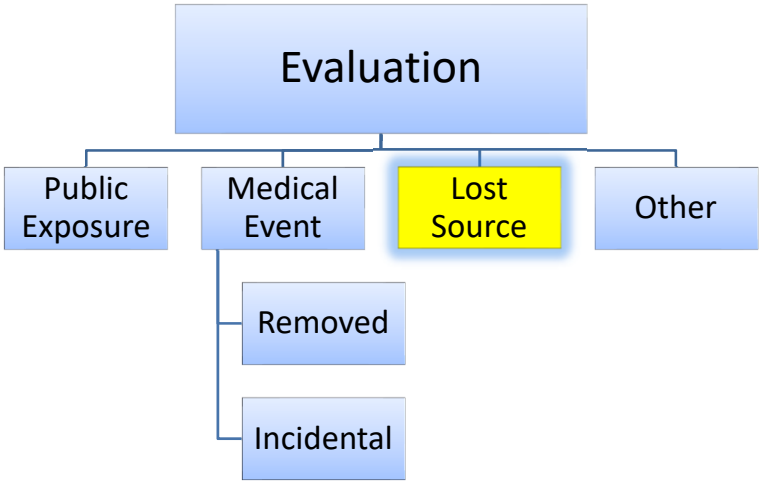
Regulatory Considerations



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Lost Source

- If the licensee is unable to retrieve a temporary source, the source could be considered lost.
- 10 CFR 20.2201 requires licensees to report loss of licensed material above specified limits.
  - Telephonic reports need to be made within 24 hours or 30 days depending on the activity.

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Lost Source (cont.)

- Written reports are required 30 days after initial telephone report and need to include:
  - Description of circumstances
  - Statement of probable disposition
  - Exposure of individuals
  - Actions taken to try to recover the material
  - Procedures to prevent another lost source

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Brachytherapy Source Accountability

- 10 CFR 35.406 requires that a licensee maintain accountability at all times for all brachytherapy sources in storage or use.
- If a source is lost, the licensee would not be able to account for the source or be able to complete the record required per 10 CFR 35.2406 for temporary implants.

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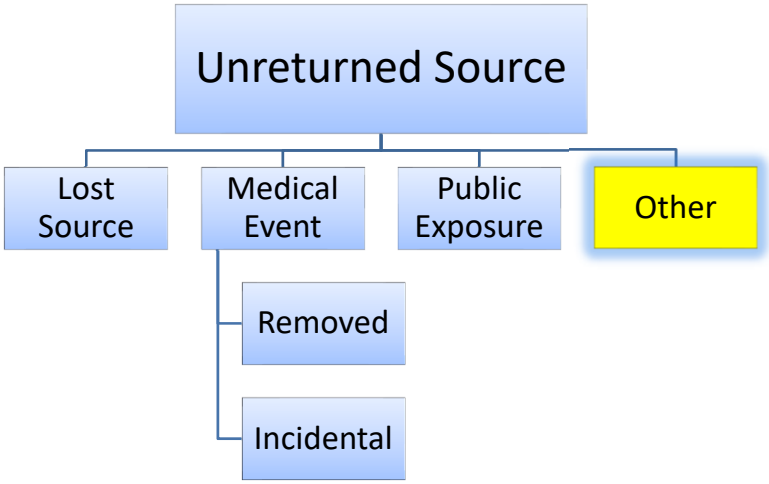
Regulatory Considerations



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Other Considerations

- Brachytherapy source accountability requires licensees to record the location of use for temporary implants per 10 CFR 35.2406.
- As the implants are temporary, the written directive will need to include dose unlike permanent brachytherapy implants which uses source strength.

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Next Steps

- Staff will continue to evaluate these regulatory questions regarding release of patients with temporary implants.
- Staff will provide ACMUI with the results of this evaluation and any associated licensing guidance documents.
- Staff will be providing AMCUI with draft 10 CFR 35.1000 licensing guidance for Alpha Dart.

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- CFR – Code of Federal Regulations
- I-125 – iodine-125
- Ir-192 – iridium-192

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ACMUI
Reporting Structure

Kellee Jamerson, ACMUI Coordinator
Medical Radiation Safety Team
March 16, 2021

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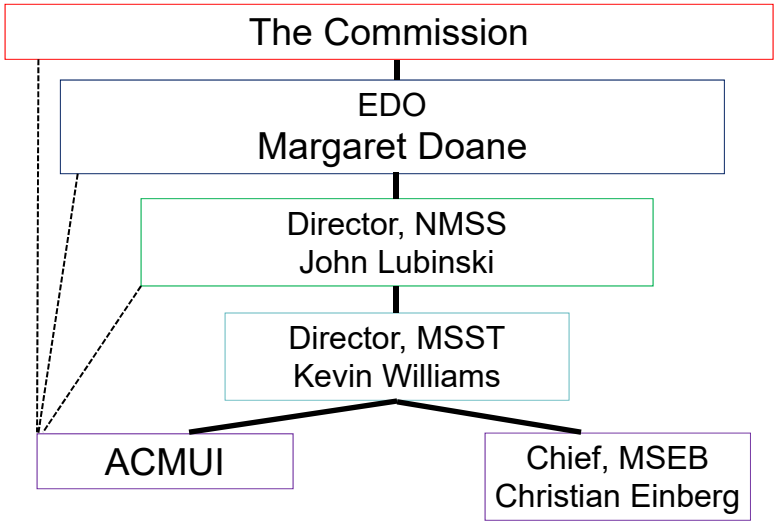
Outline

- **Current Reporting Structure**
- **Annual Review**
- **Meetings**
- **Discussion**

2

2

Current Reporting Structure



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3

Annual Review

In September 2012, the ACMUI recommended to have an annual review of reporting structure.

4

4

Meetings

Two meetings at Headquarters each year

- March/April
- September/October

Approximately 2-3 teleconferences (as needed)

5

5

ACMUI Discussion

6

6

Points of Contact

- **Kevin Williams – MSST Director**
  - **Kevin.Williams@nrc.gov**
- **Christian Einberg – Designated Federal Officer (DFO), Chief, MSEB**
  - **Christian.Einberg@nrc.gov**
- **Kellee Jamerson – DFO, ACMUI Coordinator**
  - **Kellee.Jamerson@nrc.gov**

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Acronyms

- **ACMUI – Advisory Committee on the Medical Uses of Isotopes**
- **DFO – Designated Federal Officer**
- **EDO – Executive Director for Operations**
- **MSST – Division of Materials Safety, Security, States, and Tribal Programs**
- **MSEB – Medical Safety and Events Assessment Branch**
- **NMSS – Office of Nuclear Material Safety and Safeguards**

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8

Calibration Procedures for Brachytherapy Sources

Professor Larry DeWerd, PhD, FAAPM
Medical Radiation Research Center
Dept of Medical Physics (SMPH)
University of Wisconsin
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1

Quantities for Brachytherapy Sources

- The desirable quantity is absorbed dose to water. This quantity is determined from AAPM TG 43
- The calibration quantity is air kerma strength which is converted with a dose rate constant
- Note that the quantity activity is NOT used for brachytherapy sources.
- Air kerma strength is quantity of radiation emitted from source after cladding

2

Output Quantities Traceable to NIST (Units)

- Photon Source: Air kerma strength - symbol S_k. Given as unit "U" where U[=]μGy- m^2/h. Values of S_k can be up to 260 U.
- Beta sources:
  - Absorbed dose rate in water at a depth done with an extrapolation chamber (usually 2 mm)
- I will cover photon sources because of time constraints and then some future calibrations

3

Brachytherapy Sources Division

- Low energy photon sources (both high and low dose rate)
- High energy photon sources (used for High Dose rate brachytherapy - both high and low dose rate)
- Beta brachytherapy sources (used for Intravascular Brachytherapy for prevention of restenosis, eye plaques for tumors and Ophthalmic Applicators used to treat eye)
- Majority use in Brachytherapy is Low energy – low dose rate and High energy – high dose rate

4

Brachytherapy Sources Division: Photon Sources

Energy	Dose Rate	Type	Primary calibration standard at NIST
Low	Low	LDR seeds, ^{125}I, ^{103}Pd, ^{131}Cs	WAFAC
High	High	HDR afterloaders (^{192}Ir)	Ion Chamber 7-Distance Technique

5

NIST Brachytherapy Calibration Procedures

1. Use of a free air chamber (WAFAC) for Low energy Low Dose sources
2. Use of a “thimble chamber” in air (UW) for High energy High dose sources
3. Use of an extrapolation chamber for beta sources.

6

Quantification of Radiation Absorbed Dose

- To provide effective treatment to neoplastic disease must quantify dose to tissue of interest
- Standard should be specified by a clinically relevant metric
  - Presently this quantity is air-kerma strength for photon sources. In Europe, the quantity is Reference Air Kerma Rate (RAKR)
  - The quantity is Energy deposited per unit mass (i.e. J/kg) at a distance in vacuo

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Calibration Quantities and Units (continued)

- Air Kerma Strength ($\mu Gym^2/hr$)
  - Actual characterization of source *output* in terms of the *dose* delivered to air. Related to exposure primarily by W/e, which is the average energy required to produce an ion pair in dry air.
- Endorsed by the AAPM for use in treatment planning protocols and adopted in TG 43.

8

Calculation of Dose from Air Kerma strength – uses TG 43

- $\dot{D}(r,\theta) = S_K \Lambda \left(\frac{G(r,\theta)}{G\left(r=1,\theta=\frac{\pi}{2}\right)} \right) g(r) F(r,\theta)$
- S_K is air kerma strength
- G is geometry factor
- Λ is dose rate constant
- g is radial dose function
- F is anisotropy function

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Determination of Quantities for the Clinic

- Air Kerma Strength - Determined in clinic by a well chamber traceable to NIST
- Dose rate constant, Λ, measured by TLD and Monte Carlo calculated.
- Radial dose function, g(r), and anisotropy function, F (r,θ) are all measured by TLD and calculated by Monte Carlo. G is the geometry factor
- All are consensus values.

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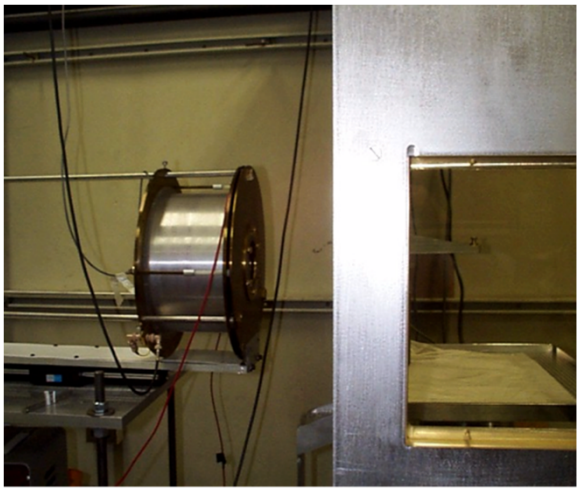
NIST Wide Angle Free Air Chamber (WAFAC)



11

Quantity and calculation for Low Energy X-ray Brachytherapy

- For x-ray sources: standard is at 50 cm in air – equation modified somewhat
-
- $\dot{D}(r,\theta) = \dot{K}_{50cm}\chi_i^{50cm}\left(\frac{G(r,\theta)}{G(1cm,\theta\frac{\pi}{2})}\right)g_i F_i(r,\theta)$
- Lamperti FAC used

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Importance of Brachytherapy Source Calibration for Clinics

- Medical physicist needs to calibrate source or if multiple sources at least 10% of the sources
- For LDR sources, there have been examples of dead seeds, some seeds with twice the output of the others in the batch.
- Don't just trust what manufacturer has sent. Measure it!!!!
- Calibration differs among sources because of cladding – 5% differences

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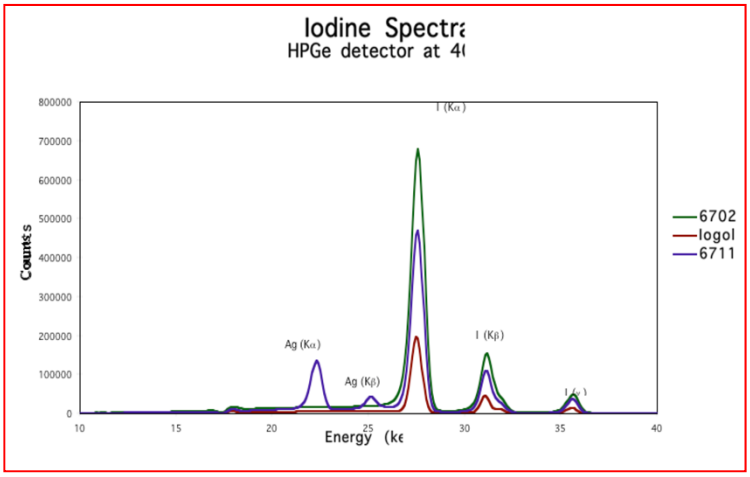
^{125}I Spectra for 3 types of seeds



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NIST Absolute Standards for LDR seeds

- NIST has transferred calibrations to ADCLs for LDR sources. all ADCL Secondary Laboratories fall within ± 0.6%
- ADCLs have traceability to NIST.
  - Beta sources: All ADCL secondary Laboratories fall within ± 2%
  - Uncertainties for Proficiency tests
    - Gamma sources: ± 2% (k=2)
    - Beta sources: ± 3% (k=2)

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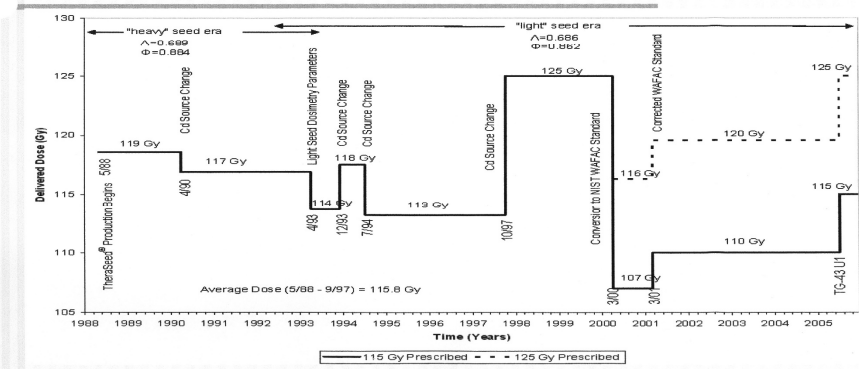
Example of ^{103}Pd source

- Palladium 103 introduced in 1987 with NO NIST standard – used a Cd source
- Manufacturer changed calibration using a different Cd source, self-shielding of the source encapsulation was different
- This resulted in a sudden 9% shift in calibration. Manufacturer communicated this by letter to users in 1997

16

Analysis of calibration variation over the years by Wayne Butler, Wheeling Hospital

Variation of ^{103}Pd delivered dose for a prescribed dose of 115 Gy (and 125 Gy after 2000)



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Palladium-103 shows the importance of having a correct calibration

- **Palladium 103 dose has changed many times.**
- **Manufacturer caused 9% shift in calibration and dose to patient.**
- **Shows importance of a standard and that physicists calibrate the sources.**

18

Brachytherapy Metrology

- Clinical calibration using a well chamber. The insert is part of the calibration.
- The chambers and methodology for brachytherapy calibrations is different from Nuclear Medicine and PET, which use a dose calibrator.
- A dose calibrator reads in activity not dose or Air kerma
- Also energy dependence of a dose calibrator is more severe than vented well chamber

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Nuclear Medicine & Dose Calibrator

- The quantity used for Nuclear Medicine and PET is activity and the unit is Bq (Curies).
- This quantity is not Dose!
- An activity may be administered by syringe but to know the dose received by a given tissue is different.
  - Expansion on this point when look at future

20

Well chambers

- ADCL Calibrated Well chamber: Provides the most convenient, accurate and precise measure of source strength.
- Know the characteristics of chamber, whether it can measure LDR or HDR or both. “What is between the source and the collector of the well?”
- Pressurized chambers (sealed) can leak 1% per year
- Use an electrometer that can measure a low enough signal without leakage for LDR sources

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Use of Well chamber

- If a single seed is used Rdg_1 is obtained
- If multiple seeds of the same strength are measured, the reading is
  $Rdg_M = n\ Rdg_1$
- If average strength per seed is needed, the total train air kerma strength is divided by the number of seeds, n.
- If strands of different strength an average is obtained.

22

Measurement through Needles

- Because of variation of thicknesses of needles (caused by manufacturer tolerances) sources have a 15% variation by needle.
- Sources cannot be measured in Needles

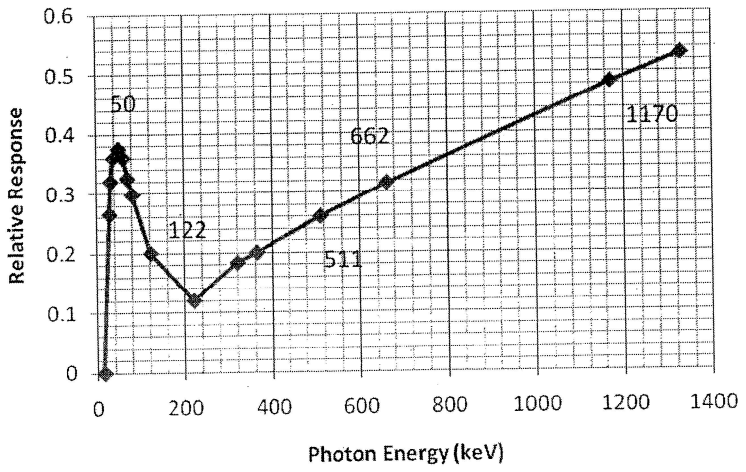
23

Energy response

- Energy response of vented chambers is not severe compared to pressurized chambers
- The following curve indicates why each energy and each chamber requires calibration

24

Energy response of sealed chambers



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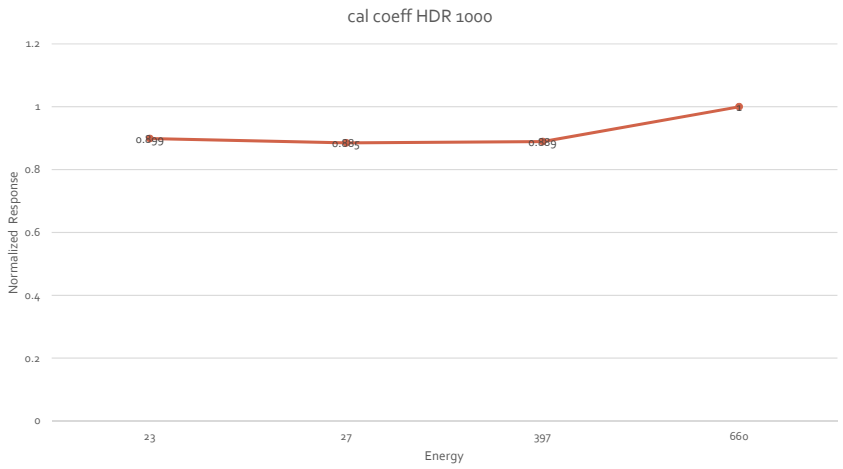
Energy response of vented chamber



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Standards for HDR and High Energy

- Higher energy sources require other techniques
- FAC are too big to use.
- A chamber with a known volume can be used or a chamber with a flat and calibrated energy response

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Calibration of ^{192}Ir HDR Sources

- NIST does not offer a primary HDR ^{192}Ir source calibration
- 7-Distance in-air technique first proposed at the University of Wisconsin by Goetsch *et al*. in 1991 – this is after the chamber calibration
- Allows ADCLs to provide NIST traceable calibrations for HDR ^{192}Ir
- NIST traceability is provided by an interpolated chamber correction factor

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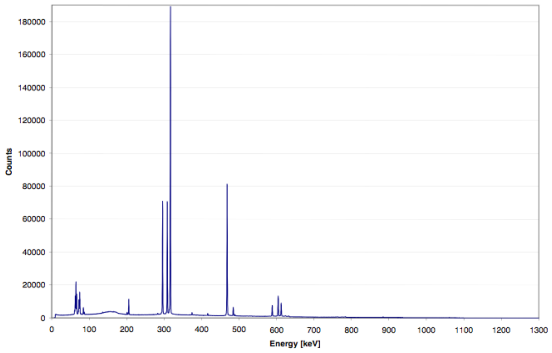
Ir-192 Spectra



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NIST traceability

- **Establishing NIST traceability requires two steps**
  - **calibration of ion chamber**
  - **using that chamber to calibrate source.**
- **Known volume chamber used by NPL.**
- **If the chamber used has a flat energy response, 2 points interpolated to the weighted average energy is all that is needed.**

30

Ionization Chamber

- The ionization chamber is calibrated at two energy points to interpolate to the weighted average energy of the HDR ^{192}Ir source, which is approximately 397 keV.
- The two points are M250 (x-ray) and Cs-137 with interpolation.
- The same buildup cap with thickness sufficient to provide CPE for highest energy must be used for both NIST calibrations

31

Interpolation methods for chamber

- Mainegra-Hing and Rogers argued that the interpolation should be based upon an interpolation proportional to ion chamber response. Thus,

$$\frac{1}{(N_K)_{^{192}Ir}} = \frac{1}{2}\left[\frac{1}{(N_K)_{M\,250}} + \frac{1}{(N_K)_{^{137}Cs}}\right]$$

- The energy for ^{192}Ir is 397 keV
- The second aspect is to calibrate the source at distances

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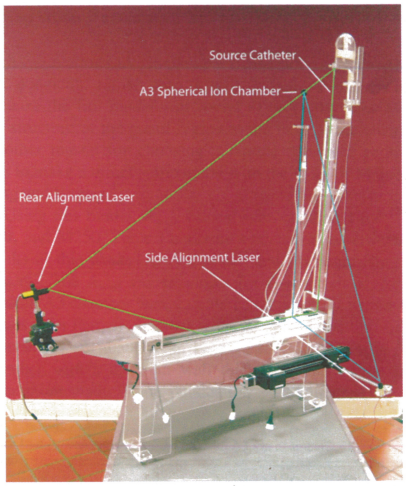
The 7-Distance Measurement Apparatus



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HDR Standards

- All primary labs do a variation on the 7-distance technique.
- NPL has a known measured volume chamber
- Others determine their factor by interpolation
- Many do all 4 coordinate directions

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HDR Sources

- There are 5 HDR sources on the market
- Monte Carlo modeling shows that there may be a difference between them.
- We investigated all sources using the 7-D technique
- Published in Med Phys 38: 6721-6729 (2011)
- UWADCL measurement was originally based on the “Classic” Nucletron HDR source

35

21 years of Measurement

- The classic Nucletron source has been measured over more than a 21 year period.
- Each individual source has been compared to the other via 3 well chambers
- The value for the well chamber after measurement by the 7 distance technique is always within ± 0.5%

36

Average for all HDR sources

HDR Source Model	% difference from Working Standard
Classic Nucletron	0.47
Nucletron V2	-0.10
VariSource VS2000	-1.13
GammaMed Plus	-0.20
Flexisource	0.89
Average for all sources	-0.01

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Comparison of HDR sources

- **When all source models are averaged the value is 0.01% compared to the 21 year old value.**
- **All source models will use the same calibration factor since all agree within 1% when the uncertainty of measurement is ±2%.**
- **Comparisons with other labs (Henri – Becquerel, NPL, PTB, NRCC) within 0.5%**
- **Summary of measurements with all sources – statistically different but all within 1% of the mean**

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Future HDR (in Europe etc.)

- Half Life of ^{192}Ir is short – replace source every 3 to 4 months.
- Use ^{60}Co have 5 years. But maintenance becomes essential
- Calibration still done as for HDR, known volume chamber at 7 distances. Calibration at cobalt energy
- Need to develop consensus values – dose rate constant, etc.

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Future

- Targeted Radionuclide Therapy Or Targeted Radiopharmaceutical Therapy (TRT)
- Alphas and betas: ^{224}Ra, Ac, Po
- Present calibration in activity
- Prefer absorbed dose to water
- Difficult since alpha and betas – how much goes to the specific area desired?

40

Future absorbed dose

- Betas calibrated with an extrapolation chamber. Windowless extrapolation chamber for beta eye plaques.
- I have a graduate student trying to do calibration for alphas and betas with a windowless extrapolation chamber – PhD thesis
- Hopefully will get Absorbed Dose to Water that would be delivered from amount of activity deposited in tissue of interest.

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Acknowledgements

- Thanks to
- Customers of MRRC whose calibrations support graduate research.
- All graduate students and staff that I have "provoked" with my thoughts.

- Any Questions.

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OPEN FORUM

No Handout

September 2021

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
29	30	31	1	2	3	4
5	6 Labor Day	7 Rosh Hashanah	8	9	10	11
12	13	14	15	16 Yom Kippur	17	18
19	20	21 Sukkot	22	23	24	25
26	27	28	29	30	1	2
3	4	Notes				

October 2021

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
26	27	28	29	30	1	2
3	4	5	6	7	8	9
10	11 Columbus Day	12	13	14	15	16
17	18	19	20	21	22	23
24 ASTRO Annual Meeting	25 ASTRO Annual Meeting	26 ASTRO Annual Meeting	27 ASTRO Annual Meeting	28	29	30
31	1	Notes				