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February 12, 2021

Kevin Williams
Director, Division of Materials Safety, Security, State, and Tribal Programs
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Delivered via email

Dear Mr. Williams,

I write to share with you and your team additional information pertinent to the extravasation topic and your team's evaluation of the petition.

- **Independent research confirms diagnostics extravasations can result in high absorbed dose.** On 2/8/21, Dr. Jeffrey Warren, the Executive Director of the North Carolina Policy Collaboratory, informed me of the results from independent research funded by the Collaboratory. This project researched if significant extravasations of routinely used diagnostic radiopharmaceuticals and a new therapeutic radiopharmaceutical could cause patient tissue absorbed doses that exceed medical event reporting limits. The results indicate patients can experience very high absorbed doses. This finding supports the cases that we have forwarded the NRC in the past, the cases included in the extravasation petition (PRM-35-22), and the approach of the novel dosimetry method described in the recent paper Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements published ahead of print in the journal *Health Physics*. Dr. Warren's email indicated that he had shared the Collaboratory report with Ms. Lopas at the NRC. I have attached the report to ensure that your team has seen this report.

- **Blood return in an IV does not guarantee a good radiopharmaceutical administration.** In the past couple of months, our customers have shared several more cases of significant extravasations. Working with the nuclear medicine centers, dosimetry was performed. Four cases (including one Ga-68 extravasation) are attached for your review and are important for several reasons. First, the dosimetry for these cases was performed in accordance with the peer-reviewed process identified in the article Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements. These patients experienced absorbed doses that exceed medical event reporting limits. Additionally, as you will see in the Notes Section of the attached dosimetry reports, often times the technologists noted the presence of blood return in the IV access catheters. This is a common misconception in the nuclear medicine community—presence of blood return in an IV does NOT ensure an ideal radiopharmaceutical administration. Leaders of the Association of Vascular Access have reviewed the public comments provided to the NRC and believe the nuclear medicine community is not following best practices to minimize radiopharmaceutical misadministrations.

- **Additional examples of how extravasations negatively affect image quality, quantification, and patient safety.** Attached is an example of a Fluciclovine F18

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extravasation. The example demonstrates how an extravasation can negatively affect image quality—in this case, a positive pelvic lymph node was not identified because of an extravasation. During Fluciclovine F18 procedures, patients are injected on the table and imaging occurs real time, and as a result, an extravasation is readily apparent. Repeat imaging of the patient revealed the positive node. Most nuclear medicine extravasations are outside of the imaging field of view and clinicians are unaware they have occurred. As a result, the vast majority of patients experiencing significant extravasations are NOT reimaged. Additionally, our team was made aware of two recent papers that demonstrate the effects of an extravasation. In the attached paper, Analysis of Unusual Adverse Effects After Radium-223 Dichloride Administration, the authors note the importance of acting quickly to manage the acute lymphedema that results from Radium-223 administration. At the time of publication, these patients had not been followed for long-term radiation injury. The paper reminds the readers that patients are not routinely imaged immediately after therapeutic radiopharmaceutical administration. The other attached paper, Masking Effect of Radiopharmaceutical Dose Extravasation During Injection on Myocardial Perfusion Defects During SPECT Myocardial Perfusion Imaging: A Potential Source of False Negative Result shows "Inadvertent faulty injection of the radiopharmaceutical and, consequently, **dose extravasation during SPECT MPI is a more important issue than that in any other diagnostic scintigraphic procedure**. As it can be considered as **a major source of false negative result**, clinician's awareness of this problem during interpretation is of great importance." (emphasis added)

- **The community does not understand the extravasation issue and mitigation steps.** The SNMMI and the SNMMI-TS noted in their position statement on extravasations and in their submitted petition comment that extravasations will now be a high priority. They stated: they are "actively addressing this as the quality-control issue that it is." In January, the SNMMI produced the attached patient leaflet, "Patient Preparation for Nuclear Medicine Procedures Involving Injections." The leaflet states that an infiltration can cause pain, redness, and swelling, but fails to mention that the radiation from an extravasation can cause longer-term tissue injury that may take years to manifest. It also suggests ice and compression as a mitigation option to reduce swelling in the case of an infiltration of a radioactive tracer, but ice and compression reduce vascular flow and would cause retention of the radioactivity rather than dispersion of the radioactivity to minimize the radiation dose to the tissue.

Two months ago, Drs. Schleipman and Jadvar misrepresented findings from two important clinical papers during the December 8, 2020 public comment WebEx. Several days later, I submitted a letter to you documenting these misrepresentations and asked you to include our letter with the transcripts from the WebEx to ensure the public would be aware of these incorrect statements. Your email reply dated December 13, 2020 agreed with my request. Recently, we were able to access the transcripts and our letter was not included. Please let me know where I can find the transcript with our letter.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ronald Lattanze
Chief Executive Officer

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Attachments:
1. Collaboratory report
2. Dosimetry paper
3. Extravasation case reports
4. Fluciclovine F18 extravasation case
5. Radium 223 lymphedema paper
6. MPI extravasation paper
7. SNMMI Patient Prep flyer

Cc: Chris Einberg
Lisa Dimmick

NC Policy Collaboratory

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February 8, 2021

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Dear Messrs. Cox and Crowley,

The North Carolina Policy Collaboratory (Collaboratory) was established by the North Carolina General Assembly (NCGA) in July 2016 to utilize and disseminate the research expertise across the University of North Carolina System for practical use by State and local government. The Collaboratory is authorized to develop and disseminate relevant best practices to interested parties, lead and participate in projects across the state related to natural resource management and other areas impacting North Carolinians, and make recommendations to the NCGA from time to time.

The Collaboratory was made aware of a North Carolina company officially petitioning the Nuclear Regulatory Commission (NRC) to eliminate an internal NRC policy circa 1980 that exempt the reporting of nuclear medicine injection extravasations, even if these extravasations meet the criteria for medical event reporting. In August 2020, the Collaboratory funded a research project to better understand whether nuclear medicine extravasations could be adversely affecting North Carolinians. The project was led by Dr. Robert Hayes at North Carolina State University (NCSU) and his graduate student Mr. Innocent Tsorxe. Dr Hayes is Certified Health Physicist with industry and field experience in radiation dosimetry and other pertinent specialties. Mr. Tsorxe is a graduate student at NCSU, president of the Health Physics Society North Carolina Chapter, and a Health Physicist at Duke University Medical Center.

Hayes and Tsorxe focused on whether extravasations of commonly used diagnostic radiopharmaceuticals and a recently approved radiotherapeutic with varying activities in varying tissue volumes could be irradiating patients with doses that exceed the NRC medical event reporting limits. New radiotherapeutics were of special interest, because of the high activity levels and the beta- or alpha-emitting nature of these therapies and the potential patient safety concerns if these therapies were extravasated.

Now that the Hayes and Tsorxe project is completed, I am including a draft manuscript of their findings in this document. I hope that you and your team find this independent research helpful in your role of reducing radiation exposure to North Carolina patients by ensuring the existence of a preeminent radiation safety culture.

Research synopsis:

> Tissue dose was calculated using Monte Carlo simulation of ^{18}F, ^{99m}Tc, and ^{177}Lu based on appropriate radiation dosimetry principles and realistic clinical parameters such as administered activity, administered volume, and biological clearance time. Results indicated that the simulated scenarios would result in tissue doses of up to several Gy. Simulation results were then validated against manual calculations as well as 3rd-party dosimetry software. **The authors concluded that based on their investigation, extravasation of both diagnostic and therapeutic radiopharmaceuticals can indeed lead to tissue doses in excess of the NRC's medical event reporting threshold** (emphasis added).

In addition to sharing these important patient safety findings with you, I am copying this letter and report to State Legislators who have expressed or might have an interest in the extravasation topic, the North Carolina Radiation Protection Commission, the NRC, the Organization of Agreement States, and Lucerno Dynamics. In addition, I encourage you to share this study with others via our website: https://collaboratory.unc.edu/current-projects/collaboratory-targeted-projects/

Sincerely,

Jeffrey Warren, PhD
Executive Director, North Carolina Policy Collaboratory
The University of North Carolina at Chapel Hill

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Dose Estimation for Extravasation of ^{177}Lu, ^{99m}Tc, and ^{18}F

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February 7, 2021

Keywords: dosimetry, internal dose, absorbed dose, radiation risk, Monte Carlo

BACKGROUND

An extravasation (also known as an infiltration) is an inadvertent injection or infusion of some or all of the radiopharmaceutical into the tissue surrounding the vein. Extravasations can happen during venous access when a catheter punctures or erodes the venous wall, or during the injection or infusion when the injection pressure damages the venous wall. The Nuclear Regulatory Commission (NRC), along with their regulatory partner the Organization of Agreement States (OAS), requires that serious misuse of medical radioactive materials be documented and reported. While reportable medical events do not necessarily indicate patient harm, they may indicate a problem with the facility's operations or at least an opportunity for improvement. In 2002, the NRC instituted a medical event reporting threshold of 0.5 Sv dose equivalent to tissue. However, a 1980 NRC policy exempts all extravasations, no matter their dose to tissue, from reporting requirements.

Between 2015 and 2017, national benchmarks were established for extravasation rates in intravenous chemotherapy infusions (0.18%) (Jackson-Rose, Del Monte et al. 2017) and contrast CT injections (0.24%) (Dykes, Bhargavan-Chatfield et al. 2015). These benchmarking studies involved multiple centers and hundreds of thousands of patients. Nuclear medicine injections, though performed under similar conditions, have been found to have much higher rates of extravasation. A review of the literature through 2017 found that three nuclear medicine centers have published six studies (Hall, Zhang et al. 2006, Bains, Botkin et al. 2009, Krumrey, Frye et al. 2009, Osman, Muzaffar et al. 2011, Silva-Rodriguez, Aguiar et al. 2014, Muzaffar, Frye et al. 2017). The average extravasation rate was 15.2% in 2,804 patients.

The 1980 NRC policy was based on a premise that extravasations were a frequent occurrence and "virtually impossible to avoid." As a result, facilities do not currently report when they extravasate patients. Additionally, dosimetry is not performed, and patients are not followed for future symptoms of harm. Furthermore, positron- and beta-emitting radiopharmaceuticals were not in widespread use in 1980. A recent publication (Osborne, Kiser et al. 2021) suggests that extravasation of diagnostic radiopharmaceuticals can result in significant dose to the injection site tissue and skin. The radiation dose to the tissue can often exceed 1.0 Sv, a level at which patients may begin to experience deterministic effects (adverse tissue reactions) (Siegel 2002) reddening of the skin, tissue ulceration, and tissue necrosis. Radiation injuries to the tissue as a result of extravasations are not immediately obvious and can take months or years to be known (Jaschke, Schmuth et al. 2017). Radiation injuries to the skin may or may not occur depending on extravasation depth, geometry, and energy emissions. Even if the skin is affected, injury may still not be visible for several days. Because dosimetry is not routinely performed for extravasations and because radiation injury is not immediate, the nuclear medicine community could be underestimating the potential harm from radiopharmaceutical extravasations.
The objective of this study was to investigate the local absorbed dose (Gy) and dose equivalent (Sv) resulting from extravasations of radionuclides commonly used in diagnostic and therapeutic procedures. Specifically, the goal is to provide a technical basis to determine whether radiopharmaceutical extravasation doses could exceed regulatory medical event reporting limits.

MATERIALS AND METHODS

Tissue dose resulting from radiopharmaceutical extravasation was estimated for ^{177}Lu, ^{18}F, and ^{99m}Tc using Monte Carlo simulation of primary emissions as well as ancillary electron emissions where appropriate. The highest local dose was estimated assuming complete interaction within the tissue volume from nonpenetrating emissions (positrons, beta particles, soft X-rays, etc.). The contribution of hard X-rays and gamma radiation was neglected (Shapiro, Pillay et al. 1987). A digital (ICRP Reference) soft tissue phantom was created using GATE[1] (GEANT4 Application for Tomographic Emission) to estimate radiation dose to a volumetric tissue. See Appendix A for an example of this code input. GATE has found widespread acceptance for simulation of human and small animal emission tomography systems including dosimetry for both internal and external radiation therapy applications (Visvikis et al. 2006). In GATE, spherical volumetric soft tissues were developed, and source activity was uniformly distributed within making it appropriate for the current study.
The approach was to apply reasonable assumptions of 25% and 50% extravasation values for injected activity along with reasonable tissue volumes. Assuming 200 mCi ^{177}Lu, 26 mCi ^{99m}Tc, and 12 mCi ^{18}F as a standard dose, the values in Table 1 were evaluated in this work.

Table 1. Extravasation initial condition assumptions.

Isotope	Clearance half-time (min)	25% Activity (mCi)	50% Activity (mCi)	Volume #1 (cm^3)	Volume #2 (cm^3)
^{177}Lu	60	50	100	20	40

[1] http://opengatecollaboration.org/, accessed 15 January 2021

^{99m}Tc	120	6.5	13	1	5
^{18}F	30	3	6	1	5

Simulation results were validated by comparison against the 3rd-party dosimetry software IDAC-Dose 2.1 (Andersson, Johansson et al. 2017), and also analytically based on the dose rate at charged-particle equilibrium. Per the Fano theorem (Attix and Roesch 1968), dose is equal to the deposited energy per mass which can be expressed as:

$$\text{Dose} = ((\text{E\_avg} * \text{A} * \text{AbsFr} * \ln(2))/(\text{T} * \text{M})) \qquad \text{Eq.1}$$

where E_avg is the average β-energy (Joules) per decay, A is activity (Bq), T is the clearance half-time (seconds) and M is the mass (kg) of the proscribed volume. When the activity is predominantly low energy beta, the absorbed fraction of emitted energy (AbsFr) is approximately unity.

A total of 12 extravasation scenarios were simulated consisting of spherical "soft tissue" material with uniform density of 1.03 g/cm^3. The simulation volumes for each scenario remained constant throughout the study. Source activity was uniformly distributed within the tissue volume and dose was calculated over the entire clearance time.

RESULTS

Figure 1 shows example emissions from the digital volumetric phantoms containing a uniform distribution of ^{177}Lu. All twelve scenarios simulated in this work indicate that tissue dose from extravasation can surpass the NRC medical event reporting threshold of 0.5 Gy. Detailed results are shown in Table 2.

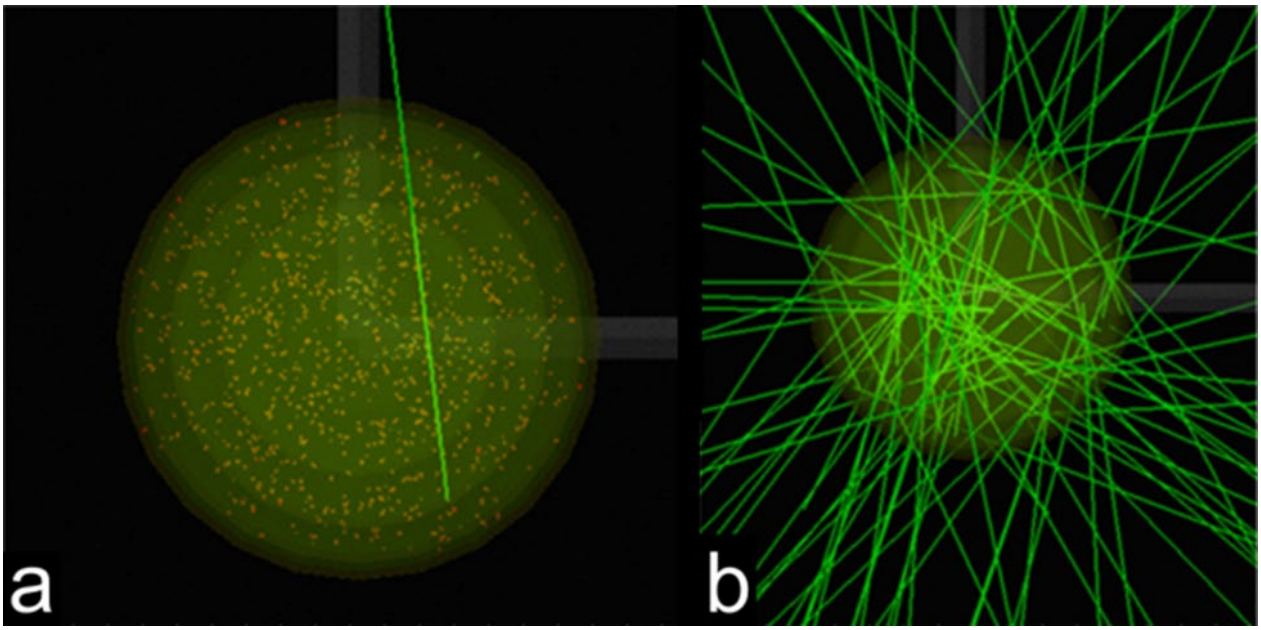

Figure 1: Digital volumetric phantoms showing emissions from ^{177}Lu including beta particle interaction (a) and gamma rays (b).

Table 2: Detailed simulation and validation results.

Radionuclide	Initial Activity (mCi)	Volume (cm^3)	Mass (g)	Clearance half-life (h)	Absorbed Dose from Simulation (Gy)	Absorbed Dose from Analytical Validation (Gy)	Absorbed Dose from IDAC-Dose (Gy)
^{177}Lu	50	20	20.60	1	12.1	9.58	10.9
^{177}Lu	100	20	20.60	1	23.5	19.2	21.8
^{177}Lu	50	40	41.20	1	5.9	6.1	5.5
^{177}Lu	100	40	41.20	1	11.6	12.1	11.0
^{18}F	3	1	1.03	0.5	7.9	7.49	7.7
^{18}F	6	1	1.03	0.5	16.2	14.9	15.4
^{18}F	3	5	5.15	0.5	1.7	1.5	1.6
^{18}F	6	5	5.15	0.5	3.5	3.0	3.3
^{99m}Tc	6.5	1	1.03	2	3.9	6.21	4.6
^{99m}Tc	13	1	1.03	2.	7.8	12.4	9.3
^{99m}Tc	6.5	5	5.15	2.	0.9	1.2	1.0
^{99m}Tc	13	5	5.15	2.	1.7	2.4	2.0

DISCUSSION

Our results suggest that extravasation of common diagnostic as well as therapeutic radiopharmaceuticals can surpass regulatory reporting thresholds. Recent research has found that extravasations can be avoided with nominal additional effort (Bonta et al. 2011). Specifically, by administering a low-activity test dose injection prior to the full administration, a simple survey can verify proper vascular circulation of the activity.

This work is relevant to patient outcomes because extravasation could be a potentially serious complication for a variety of diagnostic and therapeutic nuclear medicine procedures. Given the published rate of extravasation in nuclear medicine, a significant number of patients in the US may be subjected to unintentional injection-site irradiation exceeding the NRC's medical event reporting threshold. However, due to the NRC policy exempting extravasations from reporting, there is a lack of clinical data on this topic with respect to patient health and safety. Van der Pol et al. (2017), state "Lack of clinical follow-up after diagnostic nuclear medicine scans, but also a conservative attitude towards reporting and publishing of complications may have possibly lead to under-reporting of skin lesions." Of the 3,016 published diagnostic radiopharmaceutical extravasation cases discussed, dosimetry and patient follow-up were performed for only three; all three resulted in presentation of deterministic effects—a finding that is consistent with our results.

CONCLUSIONS

Use of therapeutic radiopharmaceuticals, such as ^{177}Lu-Dotatate, is experiencing rapid growth due to positive patient outcomes. The incidence of extravasation for these procedures is not well understood, but clearly there is a risk of significant injection site tissue dose if extravasation occurs. With prevention methods identified, consideration to adopting this or similar protocols are recommended by this work.

Future work should include more detailed modeling of doses based on realistic tissue geometries, such as proximity to bone, along with more comprehensive uncertainty estimations. Additional work on preventative measures and mitigations should also be considered.

ACKNOWLEDGEMENTS

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PATIENT-SPECIFIC EXTRAVASATION DOSIMETRY USING UPTAKE PROBE MEASUREMENTS

Dustin Osborne, PhD[1], Jackson W Kiser[2], MD, Josh Knowland[3], David Townsend[4], PhD, Darrell R. Fisher, PhD[5]

Extravasation is a common problem in radiopharmaceutical administration and can result in significant radiation dose to underlying tissue and skin. The resulting radiation effects are rarely studied and should be more fully evaluated to guide patient care and meet regulatory obligations. The purpose of this work was to show that a dedicated radiopharmaceutical injection monitoring system can help clinicians characterize extravasations for calculating tissue and skin doses.

Materials: We employed a commercially available radiopharmaceutical injection monitoring system to identify suspected extravasation of ^{18}F-fluorodeoxyglucose and ^{99m}Tc-methylene diphosphonate in 26 patients, and to characterize their rates of biological clearance. We calculated the self-dose to infiltrated tissue using Monte Carlo simulation and standard MIRD dosimetry methods, and we used VARSKIN software to calculate the shallow dose equivalent to the epithelial basal-cell layer of overlying skin.

Results: For 26 patients, injection-site count rate data were used to characterize extravasation clearance. For each, the absorbed dose was calculated using representative tissue geometries. Resulting tissue absorbed doses ranged from 0.6 to 11.2 Gy, and the shallow dose equivalent to a 10 cm^2 area of adjacent skin in these patients ranged from about 0.1 to 5.4 Sv.

Conclusions: Extravasated injections of radiopharmaceuticals can result in unintentional doses that exceed well-established radiation protection and regulatory limits; they should be identified and characterized. An external injection monitoring system may help to promptly identify and characterize extravasations and improve dosimetry calculations. Patient-specific characterization can help clinicians determine extravasation severity and whether the patient should be followed for adverse tissue reactions that may present later in time.

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BACKGROUND

Most diagnostic nuclear medicine exams and therapeutic infusions are accomplished by administering radiopharmaceuticals intravenously *(1)*. An extravasation, also known as an infiltration, occurs when a radiopharmaceutical is inadvertently injected into tissue surrounding the injection site instead of into the vasculature. Extravasations can result from improper initial placement of the intravenous (IV) access device or by failure of the vessel wall *(2)*. Extravasations occur relatively frequently (mean 10.4%, N=5418, 20 nuclear medicine centers), as previously described *(3-11)*, and can result in significant dose to underlying tissues and skin *(12-19)*. However, because radiation effects on patients may take years to manifest and are rarely studied *(19)*, dose resulting from extravasations should be more fully evaluated.

Factors that influence tissue absorbed dose from extravasation include infiltrated tissue volume as well as radioactivity distribution, retention, absorption, and clearance. Extravasation clearance rate has been estimated to be 2 to 10 hours *(20)*. Serial imaging with positron emission tomography (PET) or single-photon-emission computed tomography (SPECT) can provide more accurate estimates of radioactivity and clearance *(13,15,18,21-23)*. However, clinicians must promptly recognize that a tissue infiltration has occurred, imaging systems must be available, and staff must know how to evaluate the resulting extravasation image data. In lieu of imaging, manual serial measurements of the injection site can be made using a scintillation counter or other radiation detection system to determine retention and clearance parameters *(20)*. This manuscript describes an efficient, automated serial measurement system used to identify and characterize radiopharmaceutical extravasations.

Radiation dose estimates guide decision-making with respect to follow-up actions that may be appropriate. The purpose of this work was to show that a dedicated radiopharmaceutical injection monitoring system can help clinicians and technologists characterize extravasations for calculating tissue and skin doses.

MATERIALS AND METHODS

Radiation detector

We employed a commercially available detector (Lara® System, Lucerno Dynamics; Cary, NC, USA) to characterize 26 extravasations of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{99m}Tc-methylene diphosphonate (^{99m}TC-MDP). The Lara radiopharmaceutical injection monitoring system comprises one scintillation detector placed on the patient's skin proximal to the injection site and another on the opposite arm as a reference (Figure 1). Each detector incorporates a single bismuth germanate (BGO) crystal and a silicon photomultiplier (SiPM). The detectors are neither shielded nor collimated, so their response is omni-directional. Photon energy response is variable, depending on

radionuclide, as previously described *(24)*. Each Lara detector records photon counts per second (cps) and generates a plot of counts versus time. Reference detector output may be subtracted from injection-site detector output to correct for background photon counts such as from photons originating in the patient's torso.

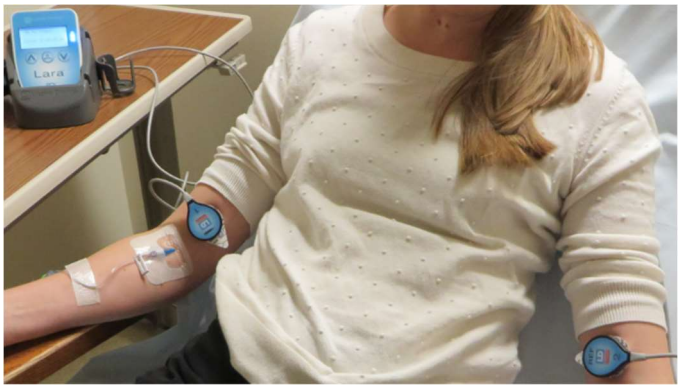

Figure 1. Photo of the injection monitoring system used on a nuclear medicine patient.

Radiation dosimetry

Using mathematical methods *(25)* recommended by the special committee on Medical Internal Radiation Dose (MIRD) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), we calculated radiation absorbed doses (Gy) to representative volumes (cm^3) of subdermal tissue containing infiltrated radiopharmaceutical. Using a slightly modified version of VARSKIN 6.1 *(26)*, a computer code for skin dosimetry, we also calculated the shallow dose equivalent (Sv) to the highest relevant area of the skin (10 cm^2).

In the MIRD formalism, the absorbed dose $D(r_T \leftarrow r_S)$ from activity in a source region that irradiates a target region is $D(r_T \leftarrow r_S) = \tilde{A}(r_S, \tau)\, \Sigma_i\, \Delta_i\, \varphi_i(r_T \leftarrow r_S) \,/\, m_T$, where $\tilde{A}(r_S, \tau)$ is the time-integrated activity in the source region, and $\tilde{A}(r_S, \tau) = \int_0^\tau A(r_S, t)dt$, where Δ_i is the mean energy emitted per decay or transformation, where $\varphi_i(r_T \leftarrow r_S)$ is the absorbed fraction (fraction of energy emitted from a source region that deposits in a target region), and where m_T is the mass of the target region *(25)*. When calculating absorbed dose to infiltrated tissue, the source and target regions are the same ($r_T = r_S$), that is, the self-dose to infiltrated tissue.

Count-rate curve

To determine the time-dependent number of radioactive decays in the source region from an extravasation, we used the Lara detector count-rate curve which reflects the "effective" disappearance of infiltrated activity (combined effects of radioactive decay and biological clearance). We then identified an appropriate mathematical function for the curve and best-fit parameters by least-squares regression analysis using commercially available curve-fitting software *(27)*. We integrated analytically to yield area under the fitted curve representing total counts from injection through complete disappearance.

Converting counts to activity present

Detector photon count rate can be converted to absolute activity (MBq) using a three-dimensional region of interest (ROI) within the patient's nuclear medicine image. We determined an activity calibration factor by dividing the fitted curve at imaging time by the ROI activity. We then converted the fitted curve to units of activity by multiplying it by the calibration factor. In the absence of quantifiable injection-site image data (e.g., injection site outside of the imaging field-of-view) extravasated activity was estimated based on overall image quality relative to a non-extravasated infusion.

Absorbed energy fraction

In the MIRD schema, the absorbed fraction $\varphi_i(r_T \leftarrow r_S)$ can be determined experimentally using calibration sources and phantoms, or it may be calculated using Monte Carlo track simulations. Using Monte Carlo simulations, we modeled the infiltrated tissue as one of three representative tissue geometries of unit-density tissue: a) a thin, right circular cylinder having a radius (r, cm) and height (h, cm) lying beneath the dermis where the tissue volume = $\pi\, r^2\, h$ (cm^3), b) as a sphere where the tissue volume = $(4\, \pi\, r^3)^{-3}$, and c) as an ellipsoid where the tissue volume = $(4\, \pi\, a\, b\, c)^{-3}$ where a, b, and c were the radii of the ellipsoid. We calculated absorbed fractions for each representative geometry using the GEANT4 Application for Tomographic Emission (GATE)[6] Monte Carlo simulation code. Each simulation consisted of 1 MBq distributed uniformly within water.

Subdermal tissue self-dose

The mass of infiltrated tissue depends on the volume of extravasated radiopharmaceutical and penetration into the subdermal fascia. We calculated the absorbed doses (Gy) to infiltrated tissues by taking into account the tissue mass, total energy emitted in the source region, and the energy absorbed fraction according to the MIRD schema *(25)*.

Relevant skin dose

The National Council on Radiation Protection and Measurements recommends *(28)* for occupational exposure that the absorbed dose in skin at a depth of 70 μm be limited to 0.5 Gy averaged over the most highly exposed 10 cm^2 of skin. Skin dose assessments in units of shallow dose equivalent (Sv) are required by the Code of Federal Regulations in 10 CFR 20.1201(c) for a contiguous 10 cm^2 area of skin at a tissue depth of 0.007 cm (7 mg cm^{-2}). For regulatory compliance with recommended skin dose limits, the software code VARSKIN, version 6.1 *(26)* was written to calculate occupational dose from radioactive contamination on or near the skin. We applied it to patient radiopharmaceutical infiltrations. For cases involving low-LET radiations, dose expressed in units of Gy and Sv are numerically (approximately) equivalent.

Because infiltrated tissue lies beneath and adjacent to the skin epidermis, we defined the relevant target for calculating dose to overlying skin as a thin layer comprising the sensitive epithelial basal cells with an area of 10 cm^2 and at a tissue depth beneath the skin surface of 0.007 cm (70 μm or 7 mg cm^{-2}). We assumed that the dose limits to patient skin should be the same or less than those for occupational exposures. We modeled infiltrated subdermal tissue as a three-dimensional thin cylinder, and calculated the relevant skin dose using a modified VARSKIN 6.1 computer code by setting the distance between the infiltrated source tissue and the sensitive basal cell layer to 10 microns (1 mg cm^{-2}) and removing backscatter correction.

[6] OpenGATE Collaboration, http://www.opengatecollaboration.org/, accessed August 25, 2020

RESULTS

Injection site count data were recorded at a rate of one measurement per second following administration of ^{18}F-FDG and ^{99m}Tc-MDP. For each case of extravasation, recorded count data was fit to a monoexponential function defining the effective clearance half-time (physical decay and biological clearance combined). Figure 2 shows one example of recorded count rate data and the corresponding curve fit.

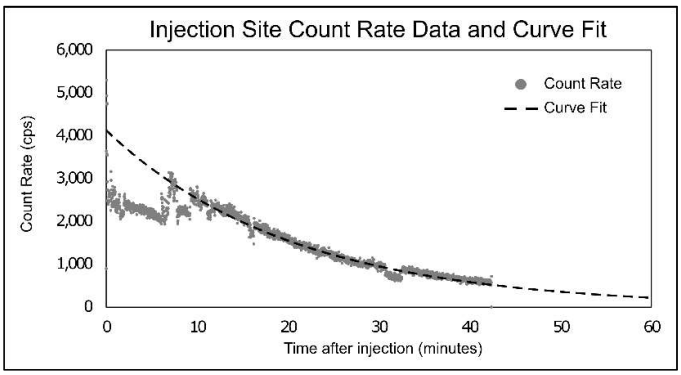

Figure 2. Injection site count rate data with curve fit for one example case.

Tissue infiltrations may present in many different shapes and sizes. Representative tissue geometries each had a mass of 5 g. Details of the tissue geometries are shown in 1. All extravasations that we evaluated exceeded tissue absorbed dose of 0.5 Gy and/or shallow dose equivalent to the skin of 0.5 Sv (Table 2).

DISCUSSION

In this work, we investigated extravasations of ^{18}F-FDG and ^{99m}Tc-MDP, but the methods described herein also apply to all other radiopharmaceuticals and amounts administered. The positron energy of ^{18}F resulted in significant tissue self-dose and significant dose to overlaying skin. Despite the relatively low absorbed fractions for ^{99m}Tc, we found that ^{99m}Tc-labeled agents can produce significant tissue absorbed doses. Our results in 26 cases exceeded commonly accepted radiation protection *(28)* and regulatory[7] limits for extremity tissue (0.5 Gy) and skin (0.5 Sv).

The literature contains several examples of adverse tissue reactions following extravasation of diagnostic and therapeutic radioisotopes such as ^{201}Tl *(19)*, ^{90}Y *(23,29)*, ^{89}Sr *(15)*, ^{131}I *(13,19,21)*, and ^{32}P *(30)*. We found one published example of radiopharmaceutical extravasation leading directly to a highly localized cancerous lesion *(31)*; following extravasation of ^{223}Ra-dichloride, the patient developed aggressive squamous cell carcinoma at the injection site.

Table 1. Representative tissue geometry details and energy absorbed fractions.

Geometry	Dimensions (cm)	Absorbed fraction for ^{18}F	Absorbed fraction for ^{99m}Tc
Cylinder	h = 0.1, r = 4	73%	11%
Ellipsoid	a = 2.13, b = 1.07, c = 0.53	95%	13%
Sphere	r = 1.07	97%	13%

Table 2. Detailed dosimetry results.

Case #	Radiopharmaceutical	Effective clearance half-time (min)	Mean absorbed dose to infiltrated fascia (Gy)	Shallow dose equivalent to skin (Sv)
1	^{18}F-FDG	9	0.6	0.3
2	^{18}F-FDG	43	7.6	3.7
3	^{18}F-FDG	93	2.7	1.3
4	^{18}F-FDG	24	8.4	4.1
5	^{18}F-FDG	13	0.8	0.4
6	^{18}F-FDG	22	0.7	0.3
7	^{18}F-FDG	44	0.9	0.4
8	^{18}F-FDG	39	11.2	5.4
9	^{18}F-FDG	70	1.0	0.5
10	^{18}F-FDG	38	8.7	4.2
11	^{18}F-FDG	22	3.8	1.9
12	^{18}F-FDG	41	0.6	0.3
13	^{99m}Tc-MDP	360	8.4	< 0.1
14	^{18}F-FDG	46	1.0	0.5
15	^{99m}Tc-MDP	64	1.5	< 0.1
16	^{99m}Tc-MDP	218	5.3	< 0.1
17	^{99m}Tc-MDP	38	0.9	< 0.1
18	^{99m}Tc-MDP	49	1.2	< 0.1
19	^{99m}Tc-MDP	64	1.5	< 0.1
20	^{18}F-FDG	18	1.1	0.5
21	^{18}F-FDG	22	5.1	2.5
22	^{99m}Tc-MDP	36	0.9	< 0.1
23	^{18}F-FDG	24	6.8	3.3
24	^{18}F-FDG	79	2.9	1.4
25	^{18}F-FDG	26	0.8	0.4
26	^{18}F-FDG	22	3.6	1.8

[7] 10CFR Part 35, Medical Use of Byproduct Material, https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/, accessed August 25, 2020

Because extravasations are common *(7)* and can lead to adverse tissue reaction, prompt identification and mitigation are important factors. In our review, none of the technologists or patients reported immediate pain or edema during or following the injection—even in cases of extravasation—emphasizing the difficulty in prompt extravasation identification. Mitigation steps such as elevation of the arm, application of heat *(32,33)*, and flushing with saline can accelerate clearance and decrease radiation doses.

Once an extravasation has been identified, accurate dose calculation enables clinicians to identify patients who should be followed for adverse tissue reactions or late stochastic effects. Absence of immediate visible skin reactions is a common explanation for not reporting and following up after extravasation events[8]. However, given the expected time for presentation of symptoms, it is unlikely that extravasation-related injury would be discovered. Van der Pol et al. reported that, despite an extensive literature review, only 3,016 published cases of diagnostic radiopharmaceutical extravasation were found. Of those, only three cases included dosimetry calculation and patient follow-up. All three patients who were followed were found to suffer adverse tissue reactions. In one case, a radiation ulcus was diagnosed after two years. In a second case, the radiation ulcus diagnosis was made after three years. Of the remaining 3,013 cases, none described dosimetric parameters or follow-up *(19)*.

In cases of ^{99m}Tc-MDP extravasation, immediate skin reactions are not likely. Our data review suggests that the shallow dose equivalent to the skin may be low even in cases where the absorbed dose to infiltrated tissue is high. Absence of prompt skin reactions should not dissuade clinicians from considering delayed detrimental effects to tissue and skin. Proper documentation and patient follow-up may protect medical institutions from frivolous litigation and unwarranted regulatory review.

CONCLUSIONS

Extravasation events in nuclear medicine are rarely fully characterized—including accurate dosimetry and appropriate clinical follow-up. Accurate dosimetry should include the determination of infiltrated fraction of administered activity, clearance half-times, and resulting radiation doses to infiltrated tissue and overlaying skin. We investigated injection-site count-rate data for 26 cases of extravasation of ^{18}F-FDG and ^{99m}Tc-MDP, assuming three source-tissue geometries. For cases reported in this paper, radiation absorbed doses to infiltrated tissue ranged from 0.6 Gy to 11.2 Gy and the shallow dose equivalent to a 10 cm^2 area of adjacent skin ranged from about 0.1 Sv to 5.4 Sv.

With patient radiation safety in mind, we maintain that both diagnostic and therapeutic extravasation events should be identified and characterized. Severe extravasations affect the diagnostic or therapeutic quality of nuclear medicine procedures, and the unintended dose to tissue and skin may eventually be clinically significant. A dedicated radiopharmaceutical injection monitoring system can be used to improve the accuracy of dosimetry and assist in determining the need for patient follow-up.

Conflicts of Interest and Funding Sources

Dustin Osborne is conducting research with Lucerno Dynamics unrelated to this manuscript and received no financial compensation for this work. Jackson W Kiser provides consultancy services for Lucerno Dynamics but received no financial compensation for this work. Josh Knowland is an employee of Lucerno Dynamics, the manufacturer of the Lara System. David Townsend has no competing interests to disclose. Versant Medical Physics and Radiation Safety (Kalamazoo, Michigan) provides consultant services to Lucerno Dynamics, but did not contribute to or receive payment for this work.

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[8] Official Transcript of Proceedings, NRC ACMUI, https://www.nrc.gov/docs/ML0903/ML090340745.pdf, accessed August 25, 2020

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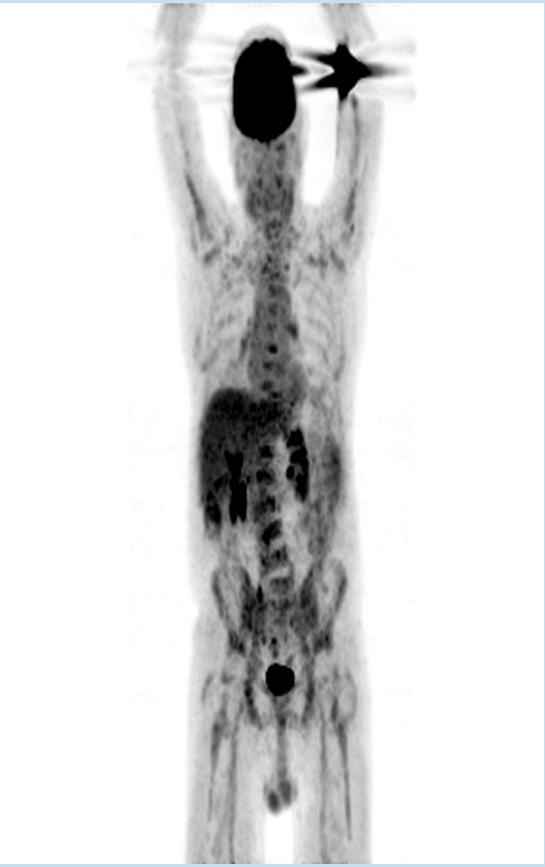
Extravasation Dosimetry Report

Scan #19952

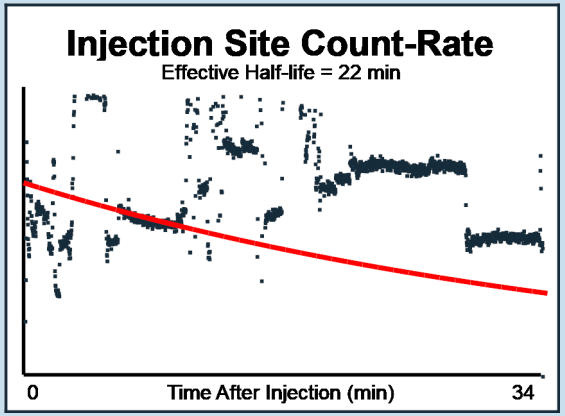


Procedure Details

Isotope	F-18
Injection method	Manual, Butterfly
Injection location	L Antecubital
Injected activity	12.80 mCi
Imaging Time	65 min

Extravasation Details

Extravasated activity	7.34 mCi (57%)
Effective half-life	22 min
Activity at imaging time	0.95 mCi

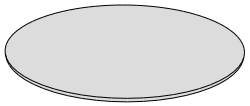


Tissue Absorbed Dose[1]

3.6 Gy

Absorbed dose is calculated for three representative tissue geometries, each with a mass of 5 g:

1. a cylinder with radius 40 mm and height 1 mm
2. an ellipsoid with radii 21.3 mm, 10.7 mm, and 5.3 mm
3. a sphere with radius 10.7 mm.



3.0 Gy

3.9 Gy

4.0 Gy

Skin Shallow Dose Equivalent[1]

Shallow dose equivalent is calculated for 10 cm² of epithelial basal skin cells.

1.7 Sv

The patient was injected with 12.8 mCi of 18F-FDG for a PET/CT scan. The technologist performing the injection reported: "Difficult IV access 23 ga butterfly provided good blood return, but was positional and infiltrated before good flush was completed."

Regarding the resulting PET imaging, the nuclear medicine physician stated: "Fortunately, the tech noticed the Lara TAC and called me before the patient was put on the table. He imaged the infiltration which is severe qualitatively by my review. He has multiple lymph nodes that are enlarged and are barely visible above blood pool as well as multiple liver lesions that are barely if at all visible above normal hepatic background."

Using methods described in the peer-reviewed paper "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" (doi: 10.1097/HP.0000000000001375), biological clearance was estimated to be 27.5 minutes and the initial extravasation activity was found to be 7.34 mCi. Therefore, absorbed dose to 5 cm^3 of tissue was estimated to be 3 to 4 Gy and shallow dose equivalent to 10 cm^2 of skin was estimated to be 1.76 Sv.

[1] This report makes use of data provided by the Lara System to calculate dose using published methods. doi: 10.1097/HP.0000000000001375
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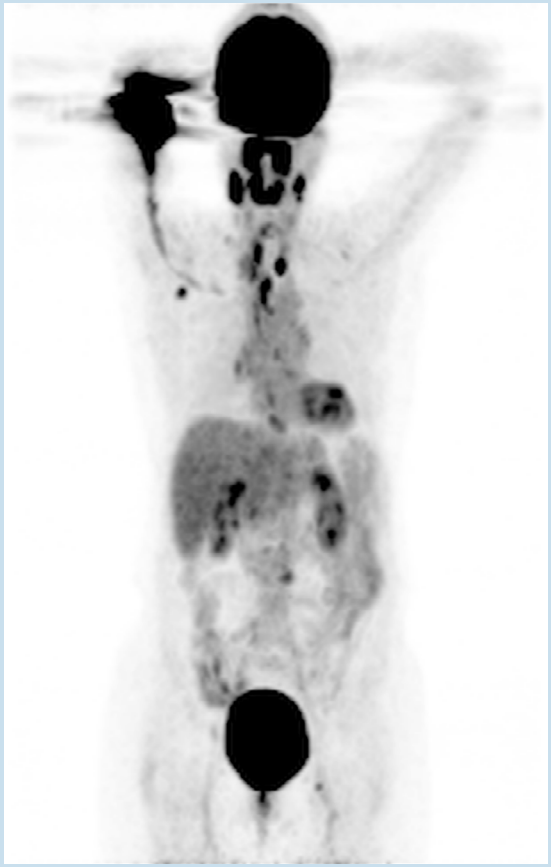
Extravasation Dosimetry Report

Scan #20954

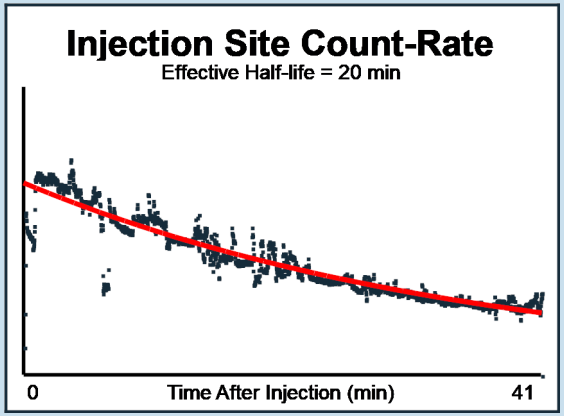


Procedure Details

Isotope	F-18
Injection method	Manual, IV
Injection location	R Antecubital
Injected activity	14.20 mCi
Imaging Time	65 min

Extravasation Details

Extravasated activity	14.20 mCi (100%)
Effective half-life	20 min
Activity at imaging time	3.87 mCi

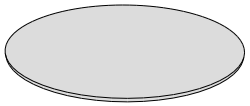


Tissue Absorbed Dose[1]

6.5 Gy

Absorbed dose is calculated for three representative tissue geometries, each with a mass of 5 g:

1. a cylinder with radius 40 mm and height 1 mm
2. an ellipsoid with radii 21.3 mm, 10.7 mm, and 5.3 mm
3. a sphere with radius 10.7 mm.



5.4 Gy

7.0 Gy

7.2 Gy

Skin Shallow Dose Equivalent[1]

Shallow dose equivalent is calculated for 10 cm² of epithelial basal skin cells.

3.1 Sv

This patient was undergoing a diagnostic 18F-FDG PET/CT study. Injection of 14.2 mCi was performed through an IV in the right antecubital. Following the injection, the nuclear medicine technologist recorded the following note: "IV place by RN [registered nurse] with US [ultrasound] guidance in patient with very difficult venous access. Good [blood] return, but burned at the end of slow dose infusion. Flush limited to 10 cc due to no blood return after 7-8 cc flush."

Using methods described in the peer-reviewed paper "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" (doi: 10.1097/HP.0000000000001375), biological clearance was estimated to be 25.1 minutes and the initial extravasation activity was found to be 14.2 mCi. Therefore, absorbed dose to 5 cm³ of tissue was estimated to be 5.4 to 7.2 Gy and shallow dose equivalent to 10 cm² of skin was estimated to be 3.14 Sv.

[1] This report makes use of data provided by the Lara System to calculate dose using published methods. doi: 10.1097/HP.0000000000001375
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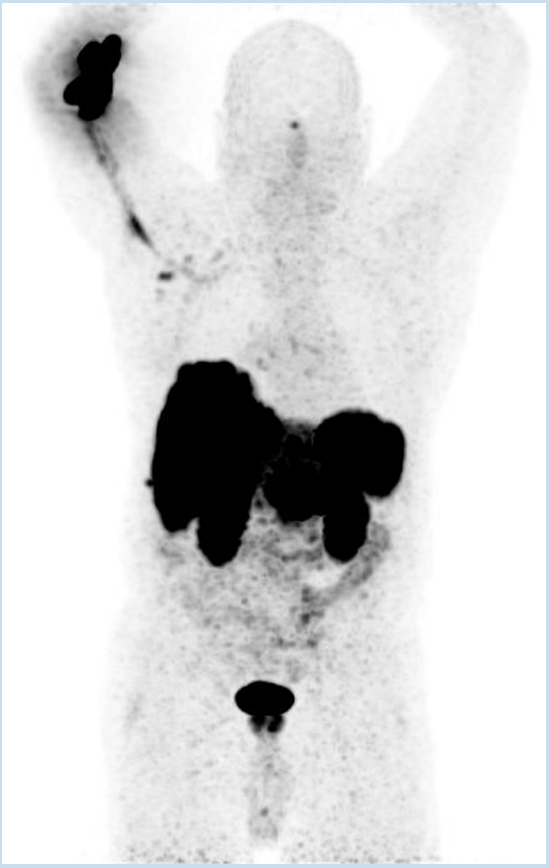
Extravasation Dosimetry Report

Scan #21373

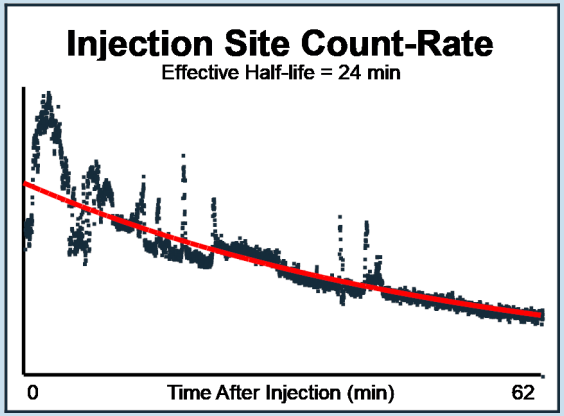


Procedure Details

Isotope	Ga-68
Injection method	Manual, IV
Injection location	R Antecubital
Injected activity	4.88 mCi
Imaging Time	68 min

Extravasation Details

Extravasated activity	3.16 mCi (65%)
Effective half-life	24 min
Activity at imaging time	0.44 mCi

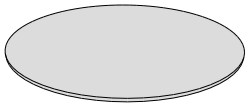


Tissue Absorbed Dose[1]

3.5 Gy

Absorbed dose is calculated for three representative tissue geometries, each with a mass of 5 g:

1. a cylinder with radius 40 mm and height 1 mm
2. an ellipsoid with radii 21.3 mm, 10.7 mm, and 5.3 mm
3. a sphere with radius 10.7 mm.



1.8 Gy

4.3 Gy

4.5 Gy

Skin Shallow Dose Equivalent[1]

Shallow dose equivalent is calculated for 10 cm² of epithelial basal skin cells.

1.3 Sv

This patient was injected in the right antecubital with 4.88 mCi of Ga-68 DOTATATE for a PET/CT scan. The technologist noted that part-way through the injection, the patient did complain of pain at the injection site and infiltration was suspected. They further noted that the IV still exhibited good blood return after the injection.

Using methods described in the peer-reviewed paper "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" (doi: 10.1097/HP.0000000000001375), biological clearance was estimated to be 36.8 minutes and the initial extravasation activity was found to be 3.16 mCi. Therefore, absorbed dose to 5 cm³ of tissue was estimated to be 1.8 to 4.5 Gy and shallow dose equivalent to 10 cm² of skin was estimated to be 1.35 Sv.

Report generated 2/11/2021 3:25:43 PM

[1] This report makes use of data provided by the Lara System to calculate dose using published methods. doi: 10.1097/HP.0000000000001375
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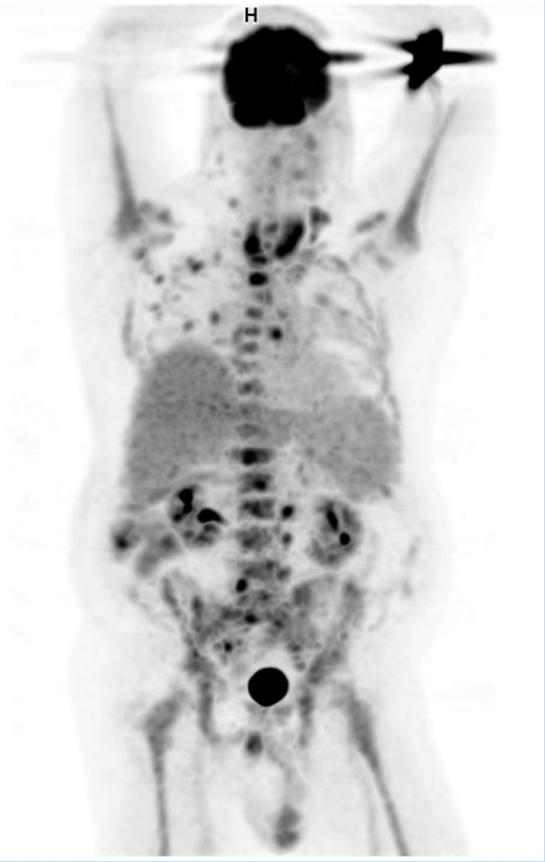
Extravasation Dosimetry Report

Scan #21537

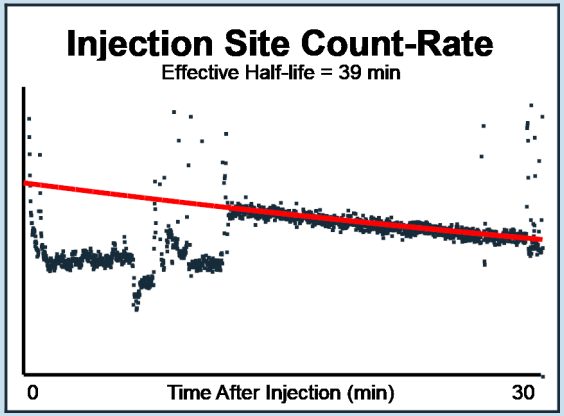


Procedure Details

Isotope	F-18
Injection method	Manual, IV
Injection location	L Antecubital
Injected activity	16.39 mCi
Imaging Time	65 min

Extravasation Details

Extravasated activity	2.79 mCi (17%)
Effective half-life	39 min
Activity at imaging time	0.87 mCi

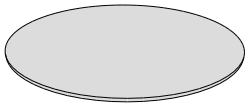


Tissue Absorbed Dose[1]

2.4 Gy

Absorbed dose is calculated for three representative tissue geometries, each with a mass of 5 g:

1. a cylinder with radius 40 mm and height 1 mm
2. an ellipsoid with radii 21.3 mm, 10.7 mm, and 5.3 mm
3. a sphere with radius 10.7 mm.



2.0 Gy

2.6 Gy

2.7 Gy

Skin Shallow Dose Equivalent[1]

Shallow dose equivalent is calculated for 10 cm² of epithelial basal skin cells.

1.2 Sv

For an 18F-FDG PET scan, the patient was injected with 16.39 mCi in the left antecubital fossa. The technologist reported that there was "good blood return", but that the IV was "positional for the flush." Additionally, upon being asked, the patient reported some stinging at the injection site.

The quality of the PET images was determined to be poor, and the patient was scheduled for a repeat PET scan.

Using methods described in the peer-reviewed paper "Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements" (doi: 10.1097/HP.0000000000001375), biological clearance was estimated to be 59.4 minutes and the initial extravasation activity was found to be 2.79 mCi. Therefore, absorbed dose to 5 cm³ of tissue was estimated to be 2.0 to 2.7 Gy and shallow dose equivalent to 10 cm² of skin was estimated to be 1.17 Sv.

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[1] This report makes use of data provided by the Lara System to calculate dose using published methods. doi: 10.1097/HP.0000000000001375
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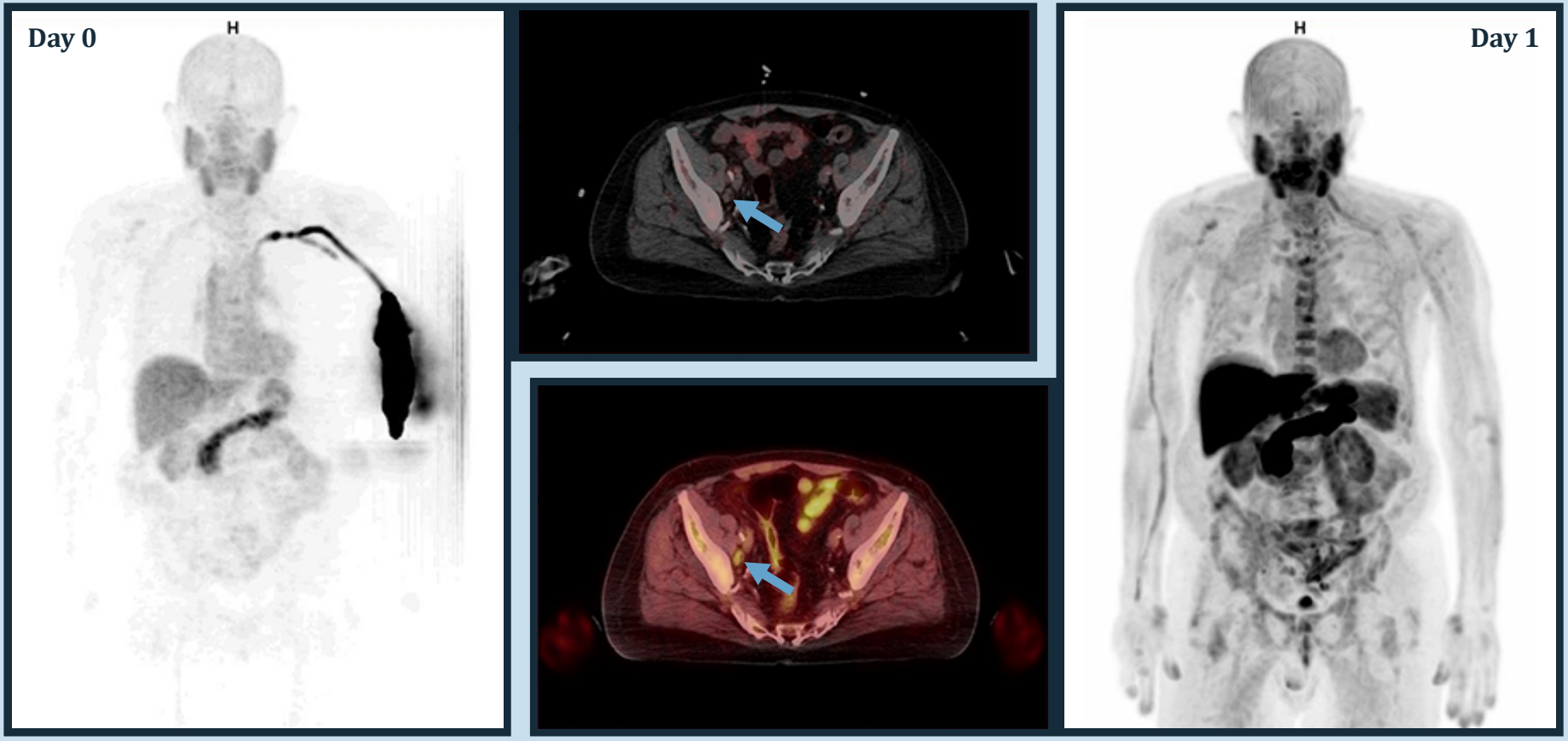
Case Report

Axumin (fluciclovine F-18) Extravasation



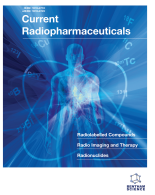
This patient had a PET/CT imaging study performed using Axumin (fluciclovine F-18) radiopharmaceutical tracer for assessment of prostate cancer recurrence.. For this procedure, the patient is injected intravenously while positioned on the PET/CT scanner table, and imaging begins immediately following injection. For this patient, extravasation of the injection resulted in poor quality, non-diagnostic images. The patient was rescheduled for the following day.

The repeat imaging study indicated uptake in a pelvic lymph node (blue arrows above) which was not visible on the previous day's extravasated images. This serves as an important example of extravasation potentially leading to misinterpretation of diagnostic studies.

Current Radiopharmaceuticals, 2020, *13*, 159-163

CASE REPORT

Analysis of Unusual Adverse Effects After Radium-223 Dichloride Administration



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Abstract: ***Background:*** To our knowledge, no previous study or literature review has been performed about the effects of the extravasation of therapeutic radiopharmaceutical agents and its potential consequences, especially regarding alpha-particle emitting radiopharmaceuticals.

Methods: Even if Radium-223 dichloride is known to be a relatively safe drug to manage, despite the correctness of the procedures applied , unexpected delayed adverse effects can occur.

In our vast experience, we rarely observed lymphedema, even after some time, at the site of administration.

Results: Management of lymphedema caused by radiopharmaceuticals administration has been addressed through clinical examples. The sudden intervention allowed a fast remission of the signs and symptoms complained by patients treated with Radium-223 dichloride.

Conclusion: The management of adverse effects after radiopharmaceuticals administration as in case of lymphedema onset, is extremely simple. These data confirm the safety of Radium-223 treatment.

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Keywords: Ra-223 dichloride, alpha particle therapy, lymphedema, life quality, radiopharmaceutical adverse effects.

1. INTRODUCTION

The growth and expansion of nuclear medicine procedures and the corresponding use of radiopharmaceuticals lead to an increase in the frequency of adverse reactions. The frequency of reported adverse effects is generally considered to be 0.1% compared to that relative to other drugs [1], so the radiopharmaceuticals are regarded as safe medicines. Nevertheless, even if quite rare, the possibility of adverse reaction to an administered radiopharmaceutical does exist. By analogy, this trending issue is involving the novel radiopharmaceutical Radium-223 and its administration. Radium-223 dichloride is an FDA-approved alpha-particle emitting therapeutic radiopharmaceutical agent indicated for the treatment of patients with castration-resistant prostate cancer (mCRPC) [2, 3], symptomatic bone metastases and no visceral metastatic disease [4]. Radium-223 is an alpha emitter with a physical half-life of 11.4 days and a whole body effective half-lives were highly dependent upon fecal compartment transfer, ranging from 2.5-11.4 d. Radium-223 decays in six steps via a chain of alpha and beta emissions into a stable isotope of lead, 207Pb. The total amount of emitted energy per the 223Ra decay series is 28.2 MeV. Alpha particles have a short path length in tissue (50-100 μm) compared with beta particles (1000-10,000 μm). The short range of alpha particle radiation allows to minimize cytotoxic damage in non-targeted cells, enabling specific cancer cell targeting with reduced toxicity to normal cells. Although Radium-223 is primarily an alpha-emitting radionuclide (> 95% of the total energy), 3.7% of the energy is emitted as beta particles and 1.1% of the energy is emitted as gamma photons. The short-range high-LEt alpha particles are responsible for the majority of the therapeutic value. A phase III study of Radium-223 dichloride in 921 patients with mCRPC and symptomatic bone metastases showed that Radium-223, compared with placebo, significantly improved median overall survival by 3.6 months, delayed the time to first symptomatic skeletal event and improves pain control and quality of life dramatically [5]. Moreover, Radium-223 had a highly favorable safety profile with a low incidence of myelosuppression [6-8]. In a phase IIa clinical trial [9] the effects of Radium-223 on bone markers, brief pain inventory (BPI) score and tumor metabolism assessed by 18F-

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1874-4729/20 $65.00+.00

fluorodeoxyglucose PET imaging provided to highlight the effectiveness of Radium-223 dichloride in treating bone metastases, even in patients with breast cancer and bone-dominant disease, combined with a minimal myelotoxicity, less than typically seen with the conventional beta-emitting radioisotopes (Samarium-153 and Strontium-89). Additional studies in patients with breast cancer are still ongoing to further investigate the efficiency and safety of Radium-223. In our center, nowadays more than 180 patients have been treated with Radium-223. We present cases of patients with prostate and breast cancer who have had unusual adverse events. This cases report was approved by the Institutional Review Board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients signed a written Informed Consent.

2. CLINICAL CASE 1

A 71 aged female with IV stage breast cancer, treated with right mastectomy and subsequent chemo-radiotherapy, currently in hormonal therapy (i.e. aromatase inhibitor), underwent Radium-223 dichloride administration for secondary bone involvement in our Nuclear Medicine Unit. During the administration of Radium-223 dichloride (about 5 MBq at the reference date, 55 kBq/kg body weight), via IV access line in the cubital region of the left upper limb, flushed prior to and after with 5ml of sodium chloride isotonic solution. Attention was paid to avoiding the IV access line on the right arm because of the relatively radical surgery sustained by patient on this side. About seven days after, the patient's left upper limb showed an evident swelling and fullness. The patient did not complain any pain in the region of injection nor in the whole left upper limb, no fever was observed, but she felt stiffness, heaviness and a reduced flexibility of the left elbow, as observed in lymphedema syndromes clinical presentation (Fig. **1**). No ulceration of the skin or subcutaneous tissue alterations were detected at physical examination, but just a slight erythema around injection site. Conventional radiological imaging [*i.e.* ultrasound and computed tomography] was carried out and there were no significant alterations of the affected arm and homolateral axillary structures (Fig. **2**). We decided to perform the long-established conservative treatment, consisting in elevation, compression bandaging and therapeutic muscular exercise to enhance lymphatic drainage. In a time frame of three weeks, the lymphedema condition and the heaviness complained by the patient gradually reverted and, at present, they did not recur. The patient is still in clinical follow up.

3. CLINICAL CASE 2

An 81 years old male, enrolled in our Nuclear Medicine Unit for radium-223 treatment for castration-resistant prostate cancer and bone secondary lesions, came to our attention about 4 weeks after the last Radium-223 dichloride administration with a moderate swelling, increase of volume of the right forearm, more pronounced in the hand and an evident pitting edema (Fig. **3**). No skin or subcutaneous tissue have been detected and the patient complained just a slight sense of heaviness. Furthermore, there were no relevant nursing or clinical issues before, apparently no extravasation occurred during or after the mentioned Radium-223 dichloride administration (about 5 MBq at the reference date, 55 kBq/kg body weight), via IV access line in the cubital region of the right upper limb, flushed prior to and after, with 5ml of sodium chloride (0,9%) isotonic solution. Moreover, the patient's clinical conditions did not show any pathologies that could be indicated as the cause of lymphedema As in the previous case, we recommended a conservative lymphatic decongestive treatment, consisting in elevation, compression bandaging and muscular exercise to enhance lymphatic drainage. The patient is currently under clinical follow-up.

4. DISCUSSION

Various national reports have been published in recent years about the occurrence of adverse effects in nuclear medicine departments after radiopharmaceutical administration [10]. The frequency of reported adverse effects is generally considered to be 0.1% compared to that relative to other drugs [1], so the radiopharmaceuticals are regarded as safe medicines. Salvatori *et al*. [11] published a meta-analysis on the occurrence of radiopharmaceuticals adverse reactions, resulting in a global incidence of $1.9 \times 10{-}5$ administrations. In a recent meta-analysis conducted by Laroche *et al*. [1], it has been showed that for all reports involving radiopharmaceuticals used with therapeutic purpose were collected 97 of

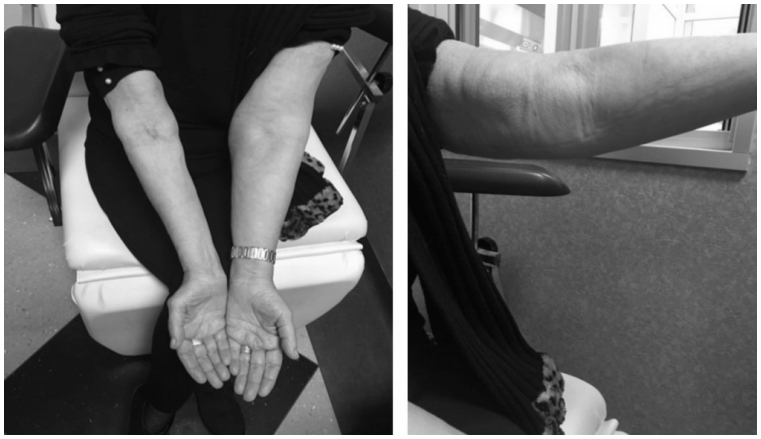

Fig. (1). Marked asymmetry between the upper limbs for significant enlargement and swelling of the left arm on clinical examination. Evident swelling of the left arm in addition to a sense of fullness and heaviness complained by patient.

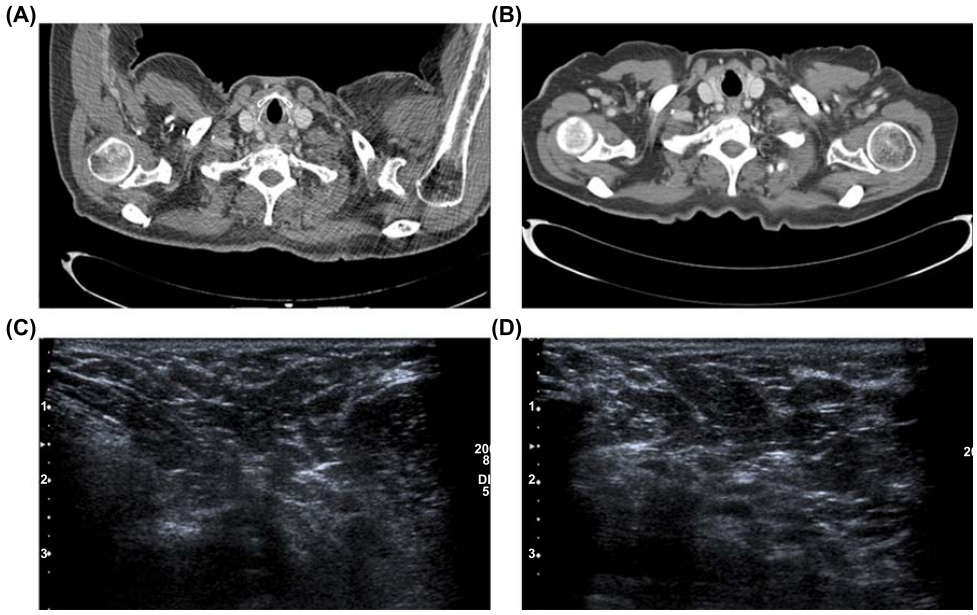

Fig. (2). Patient#1. CT scan (**A**, **B**) and US exam (**C**, **D**) images of the axillary region showing no significant morpho-structural alterations.

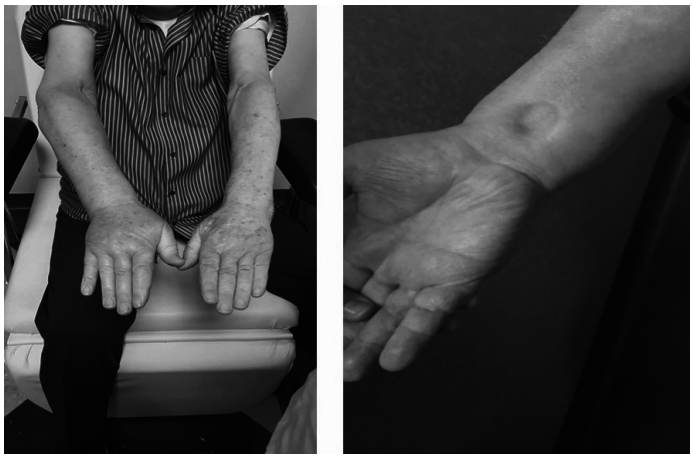

Fig. (3). Moderate swelling and increased volume of right forearm, more evident on the hand. Remarkable sign of pitting edema on the ventral side of right forearm.

adverse reactions (17.7%); pulmonary disorders were the most frequent effects reported (44.3%), usually occurred after administration of 131I-lipiodol. 153Sm-lexidronam, 90Y-ibritumomab-tiuxetan and 89Sr-chloride are accounted with a relatively much smaller prevalence.

It is widely admitted that diagnostic imaging radiopharmaceuticals are more often involved in allergic reactions, due to the carrier biochemical features, whereas radiopharmaceuticals used with a therapeutic purpose could induce rather serious adverse effects, caused by the physical properties of compound and its radiobiologic effects, therefore it should be emphasized that only to trained personnel could place iv lines before therapy. Despite the relatively wide number of studies regarding the overall radiopharmaceutical adverse effects above mentioned, we noticed a significant underreporting of the incidence and potential complications of the radiopharmaceutical extravasation or infiltration in current literature. In nuclear medicine practice, the extravasation of radionuclides results in a localized tissue retention of the radiopharmaceutical and subsequently in an unintended local radiation exposure to the regional tissues. As extravasations, particularly small ones, are frequently asymptomatic, we can postulate that their occurrence is probably underestimated. Considering the relatively high prevalence of extravasation in standard diagnostic procedures, the same might take place for therapeutic radiopharmaceuticals administration. Despite some cases of mild tissue damage following extravasation of diagnostic radiopharmaceuticals have been reported (37 publications reported 3016 cases of which 3 cases reported symptoms), extravasation of therapeutic radio compounds has the highest tendency to result in tissue damage (8 publications reported 10 cases), because of the physical characteristics of the radioisotopes used [12, 13]. In the last few years, Radium-223 dichloride has obtained marketing authorization in Europe and USA for radiometabolic treatment of patients with mCRPC and symptomatic bone metastases, as the first and, to date, only alpha emitter radionuclide. Because of that, at present, very little is known about incidence, clinical conse-

quences and eventual possible interventions after alpha emitter agents extravasation. To our knowledge, we observed thirty-four different intervention and prevention strategies performed or proposed, therefore it's self-evident a notable confusion regarding this argument. No previous study or literature review has been performed about the effects of the extravasation of commonly applied diagnostic or therapeutic radiopharmaceuticals, especially with regard of alpha emitter radiopharmaceuticals. The EANM procedure guideline for 90Y-ibritumomab tiuxetan (Zevalin®) [14] is the only guideline giving some practical advice in case of extravasation, advising local hyperthermia, elevation and massage. Other EANM and SNMMI guidelines focused on radionuclide therapy do not promote any particular practical advice in case of extravasation, regardless of the potential complications. The options of lymphedema conventional treatment include elevation, compression garments, pneumatic pumping, lymphatic massage, diuretics, surgical debulking and microsurgical reconstruction. Complete decongestive therapy (CDT) is commonly used worldwide and recommended as the clinical best practice for lymphedema medical treatment as reported in a recent systematic review [15]. Weight management, full-body exercise, information disposal, prevention and early intervention protocols are also likely to be effective [16]. Even though we experienced more than 180 patients with mCRPC and breast cancer in treatment with Radium-223 dichloride in our Nuclear Medicine Unit, and despite the correctness of the procedures applied, the clinical pictures described above were unexpected and unique events, at present unrecognized in literature and it would be worth of further consideration and investigation in the field of radiopharmaceutical extravasation. It seems appropriate to underline on the basis of these considerations, that the patient must be informed at time of therapy to watch out for possible side effects and refer to the hospital in case they appear, even in the days following administration.

On the other hand, in our experience, in which for dosimetry reasons, we obtain images of the biodistribution of 223-Ra in the days following administration, we have never observed areas of skin contamination in the area of injection.

We suggest a longstanding conservative treatment involving elevation, compression bandaging and garments and muscular exercise, in case of fever and relevant local pain occurrence, an approach with antibiotic coverage and antithrombotic heparin therapy should be preferred. These rare occasional events have confirmed the safety and simplicity of Radium-223 procedures, even in the case of unexpected events. Our experience however, underline the need for a greater and stronger knowledge regarding incidence, presentation and severity of these adverse effects with the aim of an adequate clinical response in case of extravasation, as well as for the development of more accurate guidelines covering radiopharmaceutical extravasation.

LIST OF ABBREVIATIONS

mCRPC = Metastatic Castration-resistant Prostate Cancer

MeV = Megaelettronvolt

LET = Linear Energy Transfer

BPI = Brief Pain Inventory

EANM = European Association of Nuclear Medicine

SNMMI = Society of Nuclear Medicine and Molecular Imaging

CDT = Complete Decongestive Therapy

STANDARD OF REPORTING

CARE guidelines and methodologies have been followed.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study and any accompanying images.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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Interesting Image
Mol Imaging Radionucl Ther 2018;27:141-143 DOI:10.4274/mirt.88942

Masking Effect of Radiopharmaceutical Dose Extravasation During Injection on Myocardial Perfusion Defects During SPECT Myocardial Perfusion Imaging: A Potential Source of False Negative Result

SPECT Miyokard Perfüzyon Sintigrafisi Sırasında Radyofarmasötik Doz Ekstravazasyonunun Miyokard Perfüzyon Defektlerini Maskeleme Etkisi: Olası Bir Yanlış Negatif Sonuç Nedeni

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Abstract

Proper interpretation of SPECT myocardial perfusion imaging (MPI) is primarily based on strict adherence to standard procedural protocols from patient preparation to image processing and display. Inadvertent faulty injection of the radiopharmaceutical and, consequently, dose extravasation during SPECT MPI is a more important issue than that in any other diagnostic scintigraphic procedure. As it can be considered as a major source of false negative result, clinician's awareness of this problem during interpretation is of great importance. In some occasions, no local clinical signs or image findings may be available to the interpreter to be aware of dose extravasation to adopt a suitable approach. Herein, we present a case with dose extravasation during stress phase, which is repeated another day with the same protocol, and the potential effects of dose extravasation on SPECT myocardial perfusion images from different aspects and useful image findings as hints are provided.

Keywords: Masking effect, radiopharmaceutical dose extravasation, myocardial perfusion defect, SPECT, false negative

Öz

SPECT miyokard perfüzyon görüntülemenin (MPI) doğru yorumlanması hasta hazırlığından görüntü işlenmesine ve gösterilmesine kadar her aşamada standart protokollere katı bir şekilde uyulmasına bağlıdır. SPECT MPI'de radyofarmasötiğin istemsiz olarak hatalı enjeksiyonu ve sonuç olarak doz ekstravazasyonu diğer herhangi bir tanısal sintigrafik işlemde olduğundan daha önemli bir konudur. Yanlış negatif sonucun ana kaynaklarından biri olarak değerlendirildiğinden, yorumlanma sırasında klinisyenin bu sorunun farkında olması büyük önem taşır. Bazı durumlarda, doz ekstravazasyonunun farkında olunmasını sağlayacak lokal belirtiler veya görüntüleme bulguları olmayabileceğinden yorum sırasında bu duruma uygun bir yaklaşım fırsatı olmayabilir. Burada stres fazında doz ekstravazasyonu olan bir hasta sunulmaktadır, görüntüleme aynı protokolle başka bir gün tekrarlanmıştır. Bu bulgular doğrultusunda doz ekstravazasyonunun SPECT MPI üzerinde olası etkileri farklı açılardan ele alınmış ve yararlı görüntüleme bulguları belirtilmiştir.

Anahtar kelimeler: Maskeleme etkisi, radyofarmasötik doz ekstravazasyonu, miyokard perfüzyon görüntüleme, SPECT, yanlış negatif

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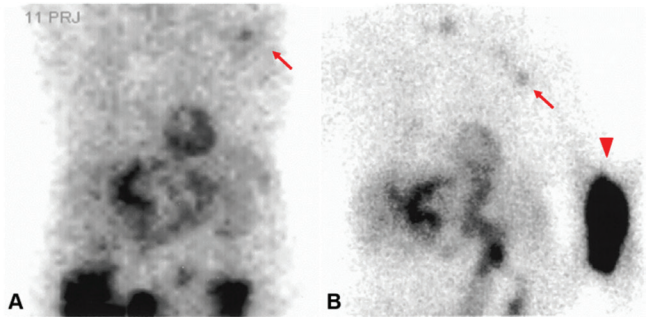

Figure 1. An 84-year-old female with a long history of asthma presented with an episode of chest pain and severe hypertension. The patient denied coronary angiography. Thus, a SPECT myocardial perfusion imaging (MPI) with dobutamine protocol was performed. Anterior projection of the raw cinematic image of stress SPECT MPI study (A) revealed a faint focal uptake in the region of left axilla (shown by arrow) as well as noticeably poor count statistics. In order to confirm the presence of tracer extravasation in the injection site, a planar anterior image with arms by the side (B) was obtained. As can be seen in B, considerable dose extravasation in the left forearm (shown by arrowhead) as well as a faintly hot axillary node ipsilateral to injection site were noted.

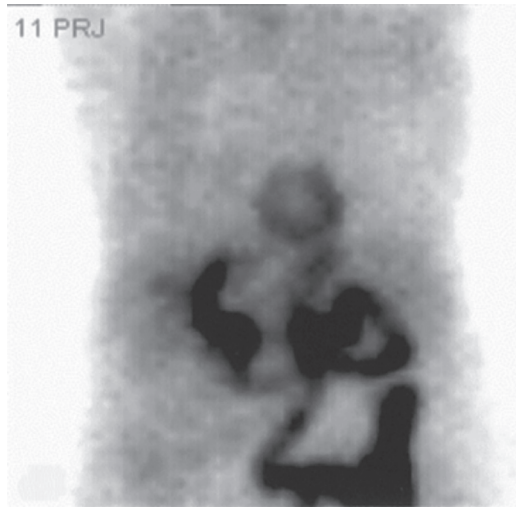

Figure 2. Anterior projection of the raw cinematic image of repeated stress study with the same protocol two days later demonstrated acceptable count statistics of the images without evidence of dose extravasation.

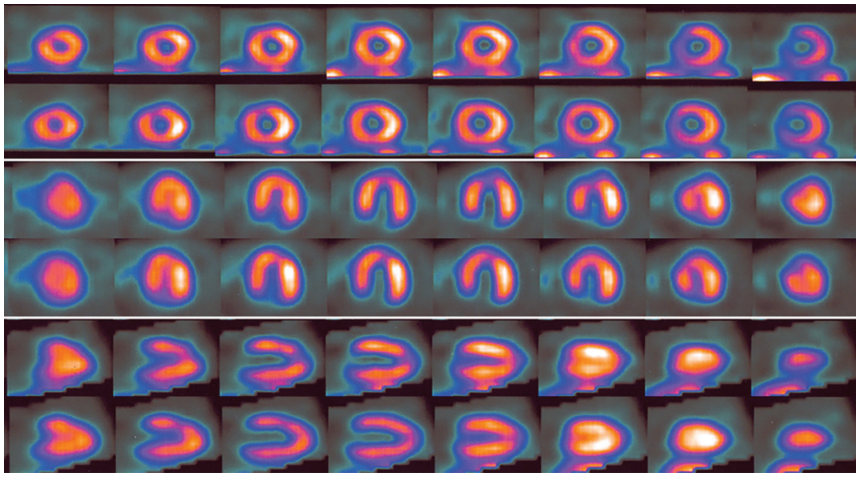

Figure 3. SPECT MPI of the initial study (upper row in each panel) and repeated study (lower row in each panel) showed a uniform tracer distribution in the initial study, but a mild perfusion defect in anterior and septal regions of left ventricular (LV) myocardium in the repeat study. From a technical viewpoint, the radiopharmaceutical with sufficient dose must be injected intravenously at peak stress during exercise or at target heart rate achieved by Dobutamine infusion. An injection with partly extravasated dose into the subcutaneous space effects the result, at least, in two possible ways. First, the amount of radioactivity entering into the circulation and then accumulating in the myocardium is insufficient that may cause a higher degree of noise in SPECT images (1). Second, which is even more troublesome, the extravasated dose gradually seeps out of the subcutaneous tissue into the circulation and then accumulates in the myocardium in the post-stress or resting condition. Therefore, the perfusion defects developing during peak stress may be attenuated or thoroughly masked (2). Moreover, the latter leads to a constantly high level of radioactivity in the background tissues. The added background counting rate and resultant higher scatter radiation are among the main factors of reducing contrast (i.e., myocardium-to-background ratio and defect-to-normal myocardium ratio). The added noise or decreased image information density as a result of lower radioactivity taken up by the myocardium contributes to impediments to visibility of defects, especially low-contrast defects (or mild perfusion defects) (3). As this issue may cause false negative interpretation and necessitates repeat of stress phase, the image should be carefully inspected for any evidence of extravasation. Although poor-count status (or grainy appearance) of the projection images and clumping of radioactivity in the myocardium (i.e., "sausage-string" pattern of LV walls) in tomographic slices (4) are considered as useful hints for dose extravasation, they are not invariably present and depend on the degree of extravasation. In patients with lower amount of extravasation, the decreased image count density might not be noticeable. Delayed images may show even better count statistics as a result of slow absorption of extravasated radioactivity (5). Another finding that implies dose extravasation is the visualization of hot axillary node ipsilateral to the injection site (6). But this is not a flawless way to discover extravasation. In some occasions, the axillary region may be out of the field-of-view and in other occasions, the node may be too faint to be readily visible. An easier and more certain way to realize possible extravasation is checking the injection site before imaging to avoid incorrect interpretation and repeating of the stress phase may be advisable.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

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PATIENT PREPARATION FOR NUCLEAR MEDICINE PROCEDURES INVOLVING INJECTIONS

Some nuclear medicine procedures involve drawing blood or receiving an injection of a tracing agent through a vein in the arm. Some patients get nervous at the thought of these procedures. The following are suggestions to help you prepare for an exam that involves venipuncture (the process of inserting a needle into a vein).

Stay well hydrated

The veins in our body contain fluid, so if you haven't had much to drink during the day, your veins may not be as easy to access and are more likely to collapse flat when a needle is inserted. (Please note that while it is helpful to be well hydrated, this may not always be possible due to certain exam preparations or medical conditions—for example if you are asked to fast or if you have fluid restrictions. As with all procedures, you should discuss preparations with your healthcare provider or the nuclear medicine technologist before the exam.)

Communicate with your health care provider

Nuclear medicine technologists are trained in venipuncture, but many have different levels of expertise. Don't be afraid to ask for a technologist who is experienced with your specific needs, such as small, deep, fragile or rolling veins.

Disclose any prior negative experiences

If you have ever passed out or felt dizzy or lightheaded after any type of venipuncture procedure, no matter how long ago, please notify the caregiver before your procedure. Often, they can have you lay down to avoid complications.

Do not smoke and avoid using products with nicotine before your exam

Nicotine is a stimulant found in cigarettes, vape, nicotine patches, and gum. It can cause your blood vessels to constrict, making it more difficult to draw blood or perform an injection. Avoid using these products immediately prior to your exam.

Dress comfortably

Often a blood draw or injection is performed in the fold of the arm. Be sure to dress in a way that allows comfortable access to that area.

What to do if swelling (hematoma) or an infiltration occurs during the venipuncture

Sometimes these things happen.

A hematoma is a swollen area filled with blood, which can occur if the needle is pierced through the vein. Compression and ice should be applied to reduce swelling, and the area should be elevated if possible. The blood from the hematoma will be reabsorbed by your body and should not cause any harm.

Infiltrations (*sometimes referred to as extravasations*) are when some of the fluid from an injection leaks into the tissue around the vein. In some cases, this can cause pain such as burning or stinging, redness, and swelling. Compression and the application of ice packs and/or warm compresses may be used to reduce swelling or to improve blood flow to the area. Depending on the type and amount of infiltration, the technologist will advise you if your exam should be rescheduled.

All venipuncture sites should be covered with a bandage to prevent infection until healed. While it is unlikely that a hematoma or infiltration will cause any harm, you should notify your primary health care provider if the pain or swelling does not decrease with time or if you notice any changes to your skin.

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