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April 2, 2019

Hon. Kristine L. Svinicki
Chair, U.S. Nuclear Regulatory Commission
Mail Stop 016-B33
Washington, DC 20555-0001

Cc: Andrea Kock
Director, Division of Materials Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards

Re: Extravasations of diagnostic radiopharmaceuticals and Medical Event Reporting

I am writing to respectfully request that the Nuclear Regulatory Commission (NRC) and the Advisory Committee on the Medical Use of Isotopes (ACMUI) re-evaluate the 1980 decision regarding extravasations and begin requiring Medical Event reporting of diagnostic radiopharmaceutical extravasations that exceed Subpart M-Reporting and Notification limits. This request supports my presentation to the ACMUI on April 3, 2019 regarding this same topic.

NRC and Extravasations

In 1980, the NRC amended the Misadministration Reporting Requirements. Details regarding this change can be found in the Federal Register Vol. 45, No. 95, Wednesday, May 14, 1980 Rules and Regulations 31701, Supplementary Information. The Supplementary Information included details regarding public comments and the NRC responses. In responding to comments, the NRC expressed several fundamental tenets regarding misadministrations:

- The reporting of misadministrations is clearly consistent with NRC regulatory responsibilities and a necessary part of an effective nuclear medicine regulatory requirement.
- Misadministrations should be reported so that causes can be identified to enable corrections and to prevent recurrence. Seemingly isolated incidents at individual medical institutions could reveal a generic problem when compared nationally.
- The significance of a diagnostic misadministration goes beyond radiation exposure to the patient if it results in misdiagnosis. Diagnostic misadministrations are of serious clinical concern because they can clearly compromise the effectiveness of the diagnostic procedure.
- The goal of the NRC is to protect patients and patients have the right to know about the risks associated with their diagnostic procedures. When patients are involved in a serious misadministration, they should be informed.
- Referring physicians should also be informed of misadministrations.

Several public comments questioned whether an extravasation should be considered a misadministration. An extravasation is the inadvertent injection of some or all of the radiopharmaceutical dose into the tissue surrounding a vein or artery. Extravasations can happen when a catheter punctures or erodes the venous wall or when the injection pressure damages the venous wall.(*1*) An extravasation results in some of the dose not being administered through the prescribed route of administration (i.e., a bolus injection into the venous system). Instead some of

the dose is administered into the tissue surrounding the vein and slowly clears through the lymphatic system. The NRC reached the decision that an extravasation should **NOT** be considered a misadministration. Their decision in 1980 was supported with the following justification: "**extravasations frequently occur in otherwise normal intravenous and intraarterial injections and are virtually impossible to avoid".**

A 1980-2002 review of the NRC position on misadministrations of radiopharmaceuticals found consistent emphasis on the importance of patient safety and a focus on the implementation of quality management programs to try to reduce misadministrations. A change to reporting thresholds was implemented (the 5-rem total equivalent dose was increased to 50-rem) as well as the introduction in August 1994 of the *Quality Management Program and Misadministration Rule*.

In 2002, the NRC amended its regulations regarding the medical use of byproduct material. Below are some discussions related to extravasations.

- The term "misadministration" was replaced with the term "medical event" (ME). In the Supplementary Information supporting the changes to the regulation, the NRC stated the misadministration term was replaced because some believe the term had "negative connotations implying negligence on the part of the physician or other hospital workers". Furthermore, "the term 'medical event' more correctly and simply conveys that the byproduct material or radiation from the byproduct material was not administered as directed by the AU".
- The Supplementary Information also described the importance of retaining "radiation protection-related requirements because of their contribution to risk reduction" as part of the 2002 Final Rule. The NRC used quality control tests for radioactivity of patient dosages as an example of a retained requirement because QC would help ensure that the dosage administered to the patient is as prescribed by the Authorized User.
- Support for notifying patients about a medical event was reinforced when the NRC stated, "We continue to believe that patient notification enables patients, in consultation with their personal physicians, to make timely decisions regarding any remedial and prospective medical care. This approach also codifies existing medical ethical standards obligating physicians to provide complete and accurate information to their patients."
- Support for requiring Authorized Users to notify referring physicians of medical events was emphasized. The NRC stated, "It is important that a referring physician is aware of medical events involving individuals. The referring physician knows the individual and his or her medical history and is likely to be in the best position to make a decision about whether informing the individual about the medical event would be harmful. That physician may also need to evaluate any follow-up actions relative to the individual's overall health history. Although notification of referring physicians may represent the "standard of care," that practice may not be uniformly followed. Therefore, the NRC retained the current requirement for a licensee to notify the referring physician about a medical event."
- The reporting and notification requirements for medical events were moved to Subpart M.
- The 50 rem or 0.5 Sievert (Sv) reporting limits were shown to correspond to the annual occupational dose limits in Part 20 and the level for reporting overexposures of workers to NRC. The Commission stated, "We believe that applying these same thresholds to reporting exposures to patients is reasonable."

In January 2008, the Boston VA hospital reported an extravasation as an ME to the NRC because the effective dose equivalent to the tissue caused by the extravasation may have exceeded the ME reporting limit of 50 rem. The NRC staff reviewed the May 14, 1980 Supplementary Information that had determined that extravasations should not be considered as misadministrations and,

therefore, concluded that the VA extravasation did NOT require reporting as an ME. As a result, the January 2008 Boston VA hospital extravasation report was retracted. Later in 2008, the NRC consulted with the ACMUI for their opinion on this NRC decision. As recorded in the ACMUI meeting minutes, both Dr. Vetter and Dr. Nag agreed that extravasations of diagnostic radiopharmaceuticals should continue to NOT be considered as misadministrations. The motion that "at this time, NRC should continue its policy of not requiring extravasations of diagnostic dosages to be reported as MEs" passed unanimously.

Today, with the help of new technology, there is evidence that nuclear medicine extravasation rates can be significantly reduced with minimal time, effort and cost, while reducing the risk of diagnostic misadministrations. This new evidence should be considered in conjunction with the long-held NRC beliefs about misadministrations and the information about extravasations that is presented in the sections that follow.

Extravasations negatively affect nuclear medicine studies

PET/CT and gamma camera images are derived from the radioactivity injected in the patient. Patients are injected with a prescribed radiopharmaceutical dose for a pre-defined uptake period to allow the radiopharmaceutical to disperse throughout the body and collect in tissue or organs before imaging begins. Imaging begins after the uptake period and when the patient is positioned with respect to the imaging equipment. When imaging begins, the detectors in PET/CT and gamma cameras start recording the gamma radiation and its distribution within the body. Computer algorithms (software) reconstruct the gamma rays into images based on the anatomic location where the rays originated and the quantity of radioactivity detected. Capturing the absolute quantification of the radiopharmaceutical distribution is one of the most valuable clinical strengths of PET imaging. This biological quantification is important for current patient care, important for precision medicine, and is a unique aspect of PET as compared with other clinical imaging modalities (e.g., CT, ultrasound, or MRI).

To create high-quality images and quantitative results, the reconstruction algorithms require manually-entered inputs, including precise information regarding the amount of radioactivity administered to the patient and the size of the patient. For nearly all procedures, clinicians require this dose be administered quickly and all at once (i.e., a bolus administration). The exact amount of uptake time the radiopharmaceutical is in circulation between the bolus and the creation of the image is also critical to image quality, quantification, and analysis. An extravasation results in radioactive dose that remains in the arm. This extravasated dose can leak back into circulation during the uptake period, degrade image contrast and quality, and contribute to inaccurate quantification. Additionally, collecting every gamma ray matters. The more counts available to the reconstruction algorithm, the better the image and the more accurate the quantification. Certain nuclear medicine scans require very low levels of injected radioactivity. Even small extravasations of these injections can have a meaningful negative effect on image quality, since the extravasated amount can represent a high percentage of the administered dose. When some of the prescribed radioactive dose is not delivered into the patient's circulation, the radiation from the undelivered dose cannot contribute to the accurate formation of images and quantification. And because the algorithm assumes the entire radioactive dose was delivered, extravasations negatively affect the resulting images and quantification results.(*2-4*) At this time, there is no way to account for, correct for, or fix an extravasation.

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Quality control (QC) exists, but not for extravasations

QC procedures for PET/CT and gamma camera scans are mandated by regulation in Europe and Australia.(*5*) In the US, QC is not mandated by regulation but is encouraged by medical societies (*6-9*) and multiple guidelines have been created for how to conduct nuclear medicine procedures. Many of these guidelines are focused on minimizing biological and behavioral factors that might adversely impact image quality and quantification. For example, in PET/CT imaging the accuracy of the dose calculations is essential for the proper reconstruction of the image. The goal of the QC steps shown in the table below is to ensure precision in the amount of dose that has been delivered into circulation and that is available for uptake. The table also describes how an extravasation affects this QC goal.

Quality Control or Protocol Process	Impact	Importance	Extravasation Effect
Measuring the residual dose left in delivery syringe after saline flush	The residual dose measurement is subtracted from the dose injected to provide a "net administered dose". The residual information affects the accuracy of the administered dose, which is an input into the PET/CT scanner and in the calculation of the Standardized Uptake Value (SUV).	Research from Osama Mawlawi, PhD at MD Anderson showed that the residual typically accounts for a 0.25% to 5% inaccuracy in the image quantification.	Same effect. Depending upon the severity of the extravasation, the quantification can be impacted from 0.25% to nearly 100%.
Entering the net administered dose into the PET/CT scanner	An incorrect entry negatively affects the calculation of the SUV.	The accuracy of the dose is critical for the quantification of the image.	Same effect. An extravasation ensures that the administered dose that is entered into the PET/CT scanner and that is used in the SUV calculation is wrong. Depending upon the severity of the extravasation, the quantification can be impacted from 0.25% to nearly 100%.
Synchronizing Clocks	Radiotracer doses are measured prior to the patient injection. The time of measurement is important in ensuring the proper decay calculation of the radioactive isotope. This impacts the accuracy of the dose and the calculation of the SUV.	Not recording the proper time that the dose was administered negatively affects the SUV.	Same effect. An extravasation results in some of the dose being delivered at a later time than intended, if it is delivered at all. This results in an understated SUV.
Delivering the dose as a bolus in first 30 to 60 seconds of the injection	A delayed or continuous injection reduces image quality and accurate quantification.	If the dose is being administered continuously throughout the uptake period then the dose remaining in the vascular system at the time of imaging is at a higher concentration than if the dose had been delivered as a bolus. This reduces the contrast and thus the image quality and sensitivity. It also negatively affects quantification because the tumor has not been exposed to the full dose for the full uptake period. This also impacts longitudinal image comparisons.	Same effect. An extravasation ensures the dose is not delivered as a bolus.

Quality Control or Protocol Process	Impact	Importance	Extravasation Effect
Uptake time from Injection to Imaging	Insufficient or inaccurate uptake time negatively affects quantification and image quality	It is essential in the comparison of two longitudinal images that the time between injection and imaging be as consistent as possible to ensure the tumor exposure to the dose is consistent. Changes in tumor uptake should be based on tumor characteristics, not on time of exposure to the dose. In addition, the length of uptake time is important to tumor uptake. The reporting of the uptake time allows clinicians to understand the implications to tumor quantification.	Same effect. An extravasation completely confounds quantification and scan comparison. When the dose is not delivered as a bolus, one cannot calculate with any accuracy the time between injection and imaging. The SUV will be understated.

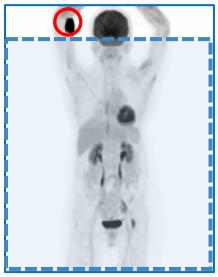
Current QC guidelines are important, are recorded, and help inform physicians regarding the quality of the diagnostic test. But current QC guidelines are missing a crucial step, ensuring that the entire administered dose enters the patient's circulation. Extravasations, which have no current QC guidelines, can have a far greater negative effect than the errors that the current QC steps are intended to address. And because extravasations often go undetected,(*10*) clinicians may unknowingly make patient management decisions using compromised images.(*11*) The only adequate solution is for a clinician to know when an extravasation happens and determine if the scan results should be used or if the scan should be repeated on a different day.

Extravasation detection

Historically, nuclear medicine extravasations have been difficult to detect during injection or upon review of the produced images. These detection difficulties are likely the result of:

- Nuclear medicine scans usually use small injection volumes of non-vesicant radiopharmaceuticals that do not cause immediate, visible changes to the overlying skin near the injection site, nor immediate pain to the patient.

- During clinician interpretation of the PET/CT images, the injection sites are often outside of the limited imaging field of view (FOV).(*10*) Area outlined by dashed blue line is the typical FOV.



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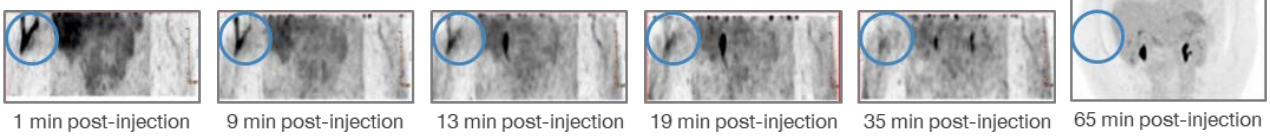
- Extravasations may have resolved (sometimes completely, see images below and right) after injection and before the image is obtained. In these situations, clinicians may not see any evidence of an extravasation on the image even when the injection site is included in the imaging FOV.(*12,13*)



Dynamic PET image acquisitions of injection site, taken during the uptake period, capture a resolving extravasation. Standard routine PET/CT image (far right) of the same patient provides no evidence of extravasation from uptake period.

Nuclear Medicine Extravasation Incidence

While not many nuclear medicine centers have reported their extravasation rates, a few have. These published and presented results support the NRC belief that diagnostic radiopharmaceutical extravasations frequently occur in otherwise normal intravenous and intraarterial injections.

- Published results – In six studies, St. Louis University, Ohio State University, and the University of Santiago in Spain have attempted to understand the magnitude of the extravasation issue by retrospectively reviewing routine static PET/CT images that were taken after the uptake period, approximately 60-90 minutes after injection. These clinical studies involved 2,804 patients and found 425 extravasations (15.2%). The PET/CT centers' extravasation rates ranged from 3-23%.(*10,14-18*) These rates are likely underestimated, due to the fact that the imaging FOV often does not include the area of the injection.(*10*)
- Soon-to-be-published Lara Quality Improvement Project - MD Anderson Cancer Center, UCLA, University of Tennessee Medical Center, Wake Radiology Services, Carilion New River Mobile, Wake Forest University, and Carilion Memorial Hospital, using Lucerno technology prospectively throughout the uptake period will report an aggregate of 2,431 patients and 150 extravasations (6.2%), with centers' extravasation rates ranging from 2-16%. Extravasation rate by technologist ranged from 0-24%.(*19*) These results likely underestimate the true extravasation rate due to the "observer" or "trial" effect, where technologists were trained on the importance of injection quality and knew that all of their injections were being monitored.
- Unpublished, presented project - All nine nuclear medicine sites (three hospitals and six centers) in Edmonton, Alberta contributed to a quality improvement project involving 450 Tc-99m MDP SPECT bone scans. They reported 79 extravasations (17.5%). The centers' extravasation rates ranged from 0-44%.(*20*)

Lucerno's early clinical work also supports the NRC belief that extravasations frequently occur. Assessments in three centers using Lucerno technology throughout the uptake period involved 393 patients and found 152 extravasations (38.7%). The centers' extravasation rates ranged from 18-40%. Extravasation rate by technologist ranged from 0-44%.

Extravasations can matter in many ways

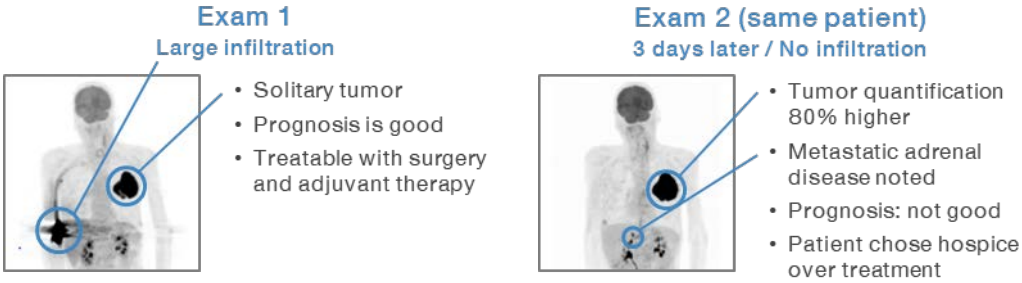
As previously noted, the NRC recognizes that the significance of a diagnostic misadministration goes beyond radiation exposure to the patient; diagnostic misadministrations are of clinical

concern because they can clearly compromise the effectiveness of the diagnostic procedure. While not all extravasations will matter acutely or to ensuing patient care, many will.

Of the three million PET/CT procedures each year in the US, over 90% are used to help oncologists diagnose, stage, choose therapy, plan treatments, assess tumor response, or longitudinally monitor cancer patients.(*21-29*) A few years after PET/CT scan reimbursement was approved by CMS, data from 40,863 PET/CT procedures performed at 1,368 centers were reported in the National Oncologic PET Registry (NOPR). The impact of PET/CT was assessed for 18 cancer types in patients with pathologically confirmed cancer. When intended management was classified as treatment or nontreatment, PET/CT images caused clinicians to change their intended management for 38% of patients. The NOPR demonstrated that PET/CT scans are a very sensitive imaging modality with respect to cancer,(*30,31*) and that the scan results play an important role in therapeutic decision-making.

Importantly, extravasations have a negative effect on the sensitivity of PET/CT. The clinical implications of an extravasation on a PET/CT study for the management of cancer patients include:

- Under-staging the disease. Leads to unnecessary (ineffective) surgery and its associated morbidity and cost, and delays initiation of necessary systemic treatment (e.g., a lung cancer patient's metastatic disease is missed (*3*) and the patient receives unnecessary surgery for what is thought to be a single lung lesion). The ways in which under-staging can occur include:
  - Failure to detect metastatic disease due to degraded PET/CT image quality and inaccurate quantification results. Due to low count rates, some metastatic disease may not be seen, or if visible, may be considered to be benign.(*11,32-35*) See example below.



  - Masked metastatic disease caused by significant extravasation artifacts in image.(*36*)
  - Misinterpreting metastatic disease, identified near an expected injection site location, as an extravasation.(*37*)
- Over-staging the disease. Leads to treatment for metastatic disease, which withholds potentially lifesaving regional therapy from the patient (e.g., an incorrect finding of metastatic disease in a lung cancer patient with a single lesion results in systemic treatment for metastatic disease rather than regional surgery or radiation therapy). The ways in which over-staging can occur include:
  - False positive lymph nodes with no obvious evidence of extravasations (due to the transport of extravasated radiopharmaceuticals through lymph channels to regional lymph nodes) may result in unnecessary invasive procedures like fine needle aspiration cytology (FNAC) or changes in chemotherapy regimens.(*32,36-54*)
  - False positive bone scans.(*55,56*)
  - Spurious lung lesions caused by radioactive clots from extravasations; such spurious lesions may require investigation by diagnostic CT and sometimes rescanning to ensure there is not a lung lesion.(*34,36,46,57-59*)

- Therapeutic procedure planning errors. Several oncologic treatment procedures rely on accurate PET/CT scans to correctly plan the therapy. For example, to plan potentially curative radiation therapy, the precise extent and location of the tumor must be known. Accurate PET/CT procedures can be crucial for the radiation oncologist to determine the patient's "planning treatment volume." Defining the gross tumor volume is the single most important step in the planning process and all other planning steps depend upon it. If the tumor is not well imaged and the gross tumor volume is not well-defined, then the entire treatment process may be futile. Oncologists use PET in target volume delineation due to its higher sensitivity and specificity compared to CT, the standard structural imaging modality. Numerous published papers show that including PET/CT information in the planning process alters treatment volumes that were originally based on CT information alone. Additionally, when patients undergo PET/CT just for radiation treatment planning, very small doses of radiopharmaceutical are used.(*60*) As previously described, small doses can be especially affected by even small extravasations. Specific examples of extravasation implications on planning include:
  - In visual assessment of the gross and clinical tumor volume, contrast of the image is very important. An extravasation can negatively affect image quality and underestimate the size of a tumor, resulting in inaccurate radiation treatment planning.(*60*)
  - In quantitative assessment of the gross and clinical tumor volume, an extravasation alters thresholds (because of lowered count rate) and therefore provides an incorrect planning treatment volume.(*60*) See patient example below where in a controlled test-retest study of results from a PET/CT scan with an extravasated injection (Day 1) and from a scan five days later with an ideal injection. The metabolic tumor volume (MTV) for four metastatic lesions were quantified.

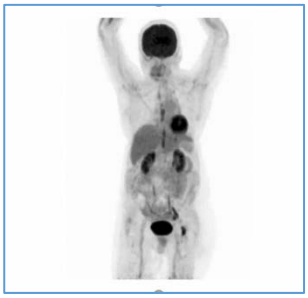
	Day 1 MTV Extravasated Injection	Day 5 MTV Ideal Injection	Understated
Lesion 1	7.43	11.34	34%
Lesion 2	5.57	10.66	48%
Lesion 3	27.77	41.07	32%
Lesion 4	0.88	2.93	70%

- Therapy assessment errors, due to understated quantification of baseline or follow-up scan.(*14,35,58,61-70*) For example:
  - An extravasated baseline study, compared with a properly injected follow-up study, may falsely indicate disease progression. Treatment may be working, but the images do not reflect this improvement. See example below. The patient was extravasated in the left hand (Day 1) and as part of a test-retest study received a second PET/CT scan 5 days later with study parameters controlled to assess the impact of the extravasation on SUV measurements of four lesions.

	Day 1 SUV Extravasated Injection	Day 5 SUV Ideal Injection	Understated
Lesion 1	5.27	10.49	50%
Lesion 2	3.97	5.94	33%
Lesion 3	7.17	11.46	37%
Lesion 4	2.62	5.73	54%

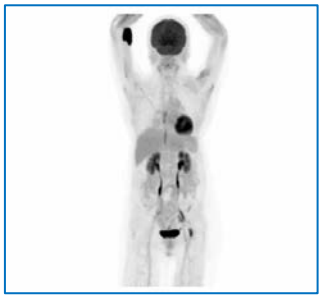
  - An extravasated follow-up study, compared with a properly injected baseline study, may falsely indicate response to treatment. Treatment may not be working, but the images suggest tumor response. See hypothetical treatment assessment example using an actual extravasated patient below:

Exam 1
No extravasation at baseline



Left pelvic lesion with SUVmax – 7.1 and an SUVmean – 4.1

Exam 2 (same patient)
Extravasation at follow up



Left pelvic lesion with SUVmax – 5.63 (21% decrease) and an SUVmean – 3.28 (20% decrease)

- Ambiguous results, caused by extravasations, unnecessarily subject the patients to invasive procedures or repeat scans, with additional radiation exposure.

PET/CT for indications other than oncology. Approximately 10% of PET/CT procedures are performed to assess myocardial perfusion, neurological function, and other physiologic processes.(*28,71*) Extravasations in these procedures can also have negative patient management implications. For example:

- A myocardial perfusion study. An extravasation on either the rest or stress exams can directly lead to either a false positive or false negative misinterpretation of the study with serious consequence for patient management.(*11,72-74*)

- An FDG neurological function study. An extravasation limits the FDG uptake in the brain and would adversely affect the reported results.(*75*)
- Amyloid plaque imaging for Alzheimer's disease and dementia diagnosis. An extravasation can cause poor image quality due to low counts and can lead to study misinterpretations.(*76*)
- Fever of unknown origin (FUO) study. FUO cases have mortality rates between 12-35% and more than 50% of these cases cannot be diagnosed using conventional imaging. PET/CT imaging shows relatively high sensitivity and specificity and can be used to improve diagnosis.(*77*) However, an extravasation may compromise imaging sensitivity and diagnostic capability.

Gamma camera. There are 15.5 million gamma camera procedures each year in the US. Extravasations of these procedures have similar implications to those found in extravasated PET/CT procedures: misinterpretation of results may lead to patient harm, unnecessary invasive procedures, and additional exposure to radiation from repeat scans. Below are some examples from published literature of gamma camera procedures and the possible implications of an extravasated injection. These examples are not intended to be comprehensive, but rather a means to illustrate the pernicious effect that extravasations can have on the quality of the resulting images and patient care.

- Kidney function. A renal scan/glomerular filtration rate (GFR) study quantifies kidney function. Extravasated injections cause false-positive findings, require repeat procedures,(*45*) invalidate GFR studies, and may not be visible in the imaging FOV.(*78,79*)
  - GFR tests are used to determine kidney donor eligibility; a falsely low GFR calculation rules out donation.
  - GFR is used to modify chemotherapy regimens based on kidney function; an affected GFR can lead to inappropriate cessation of chemotherapy treatment.
- Cardiac function. Tc-99m Sestamibi studies assess cardiac ventricular ejection fraction. An extravasated injection may compromise the study in three ways.(*72*)
  - Because less radiopharmaceutical is taken up by the myocardium, counting statistics are lowered, resulting in a scan with poor-quality images.
  - If the extravasated injection occurs during the second phase of a same-day study, the resultant second scan will be confounded by activity from the first injection. Thus, ischemia induced during a stress study may be masked—a significant error.
  - An extravasation can lead to altered distribution of the radiopharmaceutical, such as uptake in lymph nodes. Visualization of lymph node activity on the cine (dynamic) raw data images may inappropriately lead to an investigation for malignancy.
- Chemotherapy monitoring. Multigated Acquisition (MUGA) studies of the heart also assess left ventricular ejection fraction and can be used to assess the impact of a patient's chemotherapy treatment on myocardial function. An extravasation during the administration of the stannous ion compound or Tc-99m pertechnetate will result in suboptimal radiolabeling of blood cells with corresponding increased amounts of residual, unreacted free pertechnetate.(*80*) A false positive interpretation can lead to inappropriate cessation of chemotherapy treatment.
- Neurological assessment. Dopamine transporter imaging studies assess Parkinson's disease, only image the brain, and use a slow, 20-second IV injection of Ioflupane I-123. An extravasation of Ioflupane I-123 can confound the dopamine transporter study results.(*81*) In a study of 224 patients, 30 injection issues were documented.(*82*)
- Pulmonary embolism diagnosis. Ventilation Perfusion (V/Q) studies are used to diagnose the presence of pulmonary embolisms (PE), a particularly dangerous condition.
  - A V/Q scan compares two views of the lungs. The ventilation (V) image is created by breathing in air that includes a radioactive substance. The perfusion (Q) view is created by

injecting a radioactive substance with a different gamma-ray energy in an arm vein. The injection arm is out of the imaging FOV.
    - An extravasation creates the opportunity for false negative interpretations (*83*) with potential serious patient implications. In pregnant women for example, undiagnosed PE (e.g., false negative) has a mortality rate as high as 30%, which falls to 2–8% if the condition is diagnosed and treated appropriately.(*84*) If an extravasation is suspected, the study is repeated the next day with additional patient radiation exposure.(*85*)
- Bone evaluations. Planar bone scanning is one of the most common gamma camera procedures. The study requires a sharp, single-peaked bolus injection and the benefits of the study are greatly influenced by the quality of the image. A bone scan that has been compromised by an injection issue has several clinical implications:
    - Misinterpreting an extravasation for pathologic findings
    - False positive lymph node uptake
    - "Compton scatter" caused by the extravasation, leading to misinterpretation of significant breast abnormality (*86*)

In addition to the negative patient effects caused by compromising diagnostic studies, extravasations can affect patients in other ways. Using Monte Carlo simulations and actual PET data, we have concluded that some diagnostic radiopharmaceutical extravasations can exceed the Subpart M Reporting and Notification limit of 50 rem or 0.5 Sievert (Sv) effective dose equivalent to the tissue.

We investigated three radiopharmaceutical extravasation scenarios: (A) hypothetical size with activity based on tumor SUV change, (B) both size and activity based on patients' PET measurements, and (C) hypothetical size and activity. In these three simulations, no activity was modeled in the rest of the body – only the activity within the extravasation. Thus, the dose calculated is due only to the extravasation.

In example A, we simulated an actual case where the hand was out of the imaging FOV and the tumor quantification was understated by 30-74%, as observed in a controlled test-retest study designed to assess the effect of infiltrations. By knowing the injected dose and the tumor quantification changes, and by estimating the reabsorption process, we calculated how much radioactivity was extravasated into the hand. The estimated effective dose equivalent to the tissue was 11.5 Sv. In example B, we used patient data to represent how the effective dose equivalent of an extravasation can be easily underestimated by using only static PET images. In this example, by the time of imaging (107 minutes post injection) ~100 micro Curies of activity was left at the injection site. However, by monitoring this extravasation after the injection and before imaging, we know the rate at which the extravasation was resolving during the uptake period. That information, combined with an extravasation volume based from PET data, leads to an estimated effective dose equivalent to the tissue of 2.26 Sv. In example C, we created a simulation that we believe is representative of many of the extravasations we have monitored. We simulated an extravasation of 1 mCi at time of imaging with a reabsorption time of 166 minutes. The estimated effective dose equivalent to the tissue was 3.41 Sv. The engineering report that details these calculations is attached as Appendix A.

	Time between injection and imaging	Estimated extravasation activity at time of imaging	Estimated effective dose equivalent to the tissue from injection to reabsorption time
A	57 minutes	4.55 mCi	11.5 Sv (~23x limit)
B	107 minutes	0.11 mCi	2.26 Sv (~4.5x limit)
C	60 minutes	1.0 mCi	3.41 Sv (~6.8x limit)

Therapeutic radiopharmaceutical extravasations can cause severe patient injury near the injection site (*32,39*) and can also exceed Subpart M Reporting and Notification limits. Using Monte Carlo simulations to model the effects of a Lutetium-177 radiotherapeutic extravasation, we have concluded that even a small (5%) extravasation of the 200 mCi infusion can expose the tissue and skin to effective dose equivalent amounts that exceed reporting limits. The engineering report that details these calculations is attached as Appendix B.

Finally, in addition to the harm that extravasations can cause by compromising diagnostic procedures and by unnecessarily exposing tissue and skin to effective dose equivalents that exceed NRC reporting limits, known extravasations can cause patients to undergo repeat diagnostic studies, where they receive additional radiation exposure and increase costs for patients and payers.

Extravasations are avoidable

There is substantial and current evidence supporting the NRC statement: “extravasations frequently occur in otherwise normal intravenous and intraarterial injections”. In addition, there is substantial evidence that supports the NRC belief that extravasations can negatively affect diagnostic procedures and thus patient care. ***However, the NRC belief that extravasations are “virtually impossible to avoid” is incorrect***.

In injection processes for patient populations similar to nuclear medicine patient populations, monitoring and reporting requirements have led to continual quality improvement efforts, and extravasation rates have declined to low levels over time. Despite this improvement, clinicians continue to make large scale efforts to drive these rates even lower.(*87*) Chemotherapy extravasation rates in the 1980s and 1990s ranged from 3-6%.(*88,89*) A recent attempt to create a national benchmark of the chemotherapy extravasation rate assessed 739,832 patients. The overall extravasation rate was 0.10% with peripheral IV and central venous access methods contributing estimated extravasation rates of 0.18% and 0.01%, respectively.(*90*) Similar efforts to reduce non-ionic iodinated contrast medium extravasation rates have also proven successful. CT extravasation rates from 1991-2007 were 0.45%. In 2015, A National Data Registry and Practice Quality Improvement Initiative involving 454,497 CT scans showed that rates had improved to 0.24%.(*91,92*)

Low extravasation rates can also be accomplished in nuclear medicine injections. Four of the centers that participated in the Lara QI project designed quality improvement plans based on extravasation contributing factors specific to their centers and improved their extravasation rates (see table below). Their aggregated rate had a statistically significant decrease, from 8.9% to 4.6% ($p<0.0001$). These results were accomplished in approximately six to eight months from the time the centers began measuring their baseline extravasation rates. In fact, two of these centers are now approaching 1% extravasation rates.

Site	Measure Phase Rate	Standard Error	Improve Phase Rate	Standard Error	Change
A	13.3%	2.1%	2.9%	1.0%	-78%
B	15.7%	4.0%	6.0%	2.6%	-62%
C	12.8%	1.5%	8.7%	1.3%	-32%
D	2.1%	0.6%	1.9%	0,6%	-10%

Extravasations will matter even more in the future

Prevention of extravasated radioactive injections will become more important for US patients in the future for three reasons:

- Procedure volumes will increase. PET/CT and gamma camera procedures are expected to grow in volume and importance as precision medicine initiatives increase.(*28,71,93-97*) As a result, more patients will be extravasated.
- Per-procedure doses will decrease. As part of an effort to reduce radiation exposure for patients, clinicians are being asked to administer doses that are “as low as reasonably achievable” (ALARA). US clinicians currently use significantly higher doses (~2x) of PET/CT radiopharmaceutical than those in Europe and Asia. Extravasations of lower administered doses will have a greater negative effect on image quality and quantification. An extravasation of a 1 mCi dose may only have a 5% impact to a nuclear medicine study using a 20 mCi dose. However, that same 1 mCi extravasation of a study using a 5 mCi dose will result in a 20% impact to the scan results. Moving forward with the ALARA principle will result in a higher proportion of cases where extravasations potentially affect patient management.
- Use of alpha and beta emitting therapeutics is growing. As radiotherapeutics enter the US market, the stakes rise in yet another way. Radiation from alpha and beta emitters is different (half-life and distance traveled) than gamma emitters and can be more dangerous when extravasated. Even a small extravasation of an alpha or beta emitter can provide a significant effective dose equivalent to the skin (as simulated in Appendix B) and destroy the tissue at the injection site.(*98,99*)

Interested parties

Addressing the extravasation issue appears consistent with the goals of all parties involved in nuclear medicine.

Identifying, and then reporting extravasations that qualify as a medical event, and reducing the incidence of extravasations, seem consistent with NRC goals:

- To protect patients from unnecessary radiation exposure, as well as from compromised diagnostic studies.
- To receive reports, determine causes, and prevent recurrence.
- To ensure referring physicians and patients are notified of medical events that have exceeded reportable limits.

Correcting the extravasation issue is also consistent with nuclear medicine and molecular imaging societies' policies. These societies are focused on patient safety, as evidenced by their consistent public comments during the NRC's latest request concerning the training and experience levels of Authorized Users. These societies also understand that radiotherapeutic extravasations will cause acute patient harm and that the technologists extravasating diagnostic doses today will be the same technologists responsible for therapeutic injections tomorrow. Additionally, societies believe that nuclear medicine can play an important role in the practice of precision medicine; extravasations result in imprecise medicine. More specifically, the Society of Nuclear Medicine and Molecular Imaging has created an initiative focused on the "Quality of Practice". This initiative has created a goal to ensure that Society members are known for high-quality, value-driven performance and delivery of patient-centered nuclear medicine practice. Extravasations have no place in the "Quality of Practice".

Improving extravasation rates is also consistent with the goals of the personnel involved in nuclear medicine. Technologists are very interested in ensuring they are delivering ideal injections to their patients. Physicists are interested in ensuring reproducible and repeatable nuclear medicine studies. Radiation safety officers want to minimize unnecessary radiation exposure to patients. And physicians want to ensure their patients get the best care.

Certainly, patients want the highest quality nuclear medicine studies since these studies are important to their care. Patients do not want the risk of additional radiation exposure as the result of extravasations. And no one—patients, payers, or employers—wants to pay providers for compromised diagnostic studies, unnecessary procedures, or the wrong care.

Extravasation Summary

Extravasations negatively affect nuclear medicine studies. The significance of extravasations is increasing each year. While QC exists today to address some processes that may affect study outcomes, no QC exists for the critical injection process to ensure the entire administered radiopharmaceutical dose is actually delivered into the patient's circulation. Historically, detection of extravasations has been difficult, and no reporting requirements existed. As a result, extravasation rates are not only high, but approximately 60 times greater than contrast CT rates and 84 times greater than chemotherapy rates. Nuclear medicine extravasations can matter in many ways. They can negatively affect care by compromising patients' diagnostic procedures and the ensuing care. They can cause repeated imaging procedures that expose patients to unnecessary radiation exposure. And extravasations can exceed the NRC reporting limits of effective dose equivalent to the tissue. Because extravasations often go undetected or unreported, patients and their treating physicians are unaware; this can lead to misinformed care decisions. However, the current NRC policy does not consider diagnostic radiopharmaceutical extravasations reportable as medical events even when they exceed current reporting limits. This policy is based on a 1980 decision that suggested that extravasations are virtually impossible to avoid. But today, there is evidence that nuclear medicine extravasations rates can be significantly and quickly reduced by using new, low-cost, QC/QA technology seamlessly integrated into current workflows. Such an effort appears consistent with the goals of all parties involved in nuclear medicine. A suggestion for an injection-monitoring QC procedure is included as Appendix C.

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Request

To help protect nuclear medicine patients, the NRC should modify their 1980 policy based on new evidence that many extravasations can be detected, and ultimately avoided. In the future, nuclear medicine injections should be monitored and any therapeutic **or** diagnostic radiopharmaceutical extravasation that meets the medical event reporting requirements of 10 CFR Part 35.3045 Subpart M should be reported and notifications made.

Sincerely,

Ronald K. Lattanze

Digitally signed by Ronald K. Lattanze
DN: cn=Ronald K. Lattanze, o=Lucerno Dynamics, LLC, ou, email=rlattanze@lucernodynamics.com, c=US
Date: 2019.04.02 14:36:12 -04'00'

Ron Lattanze
Chief Executive Officer

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Appendix A: Equivalent Dose due to Diagnostic Radiotracer Extravasation—a Monte Carlo Investigation

Background

An intravenous extravasation is when an injected substance leaks into surrounding tissue instead of remaining within the vasculature as intended. It can be caused by improper placement of the IV, erosion or degradation of the vessel wall, or failure of vessel integrity*(1)*. When a diagnostic radiopharmaceutical is extravasated, a percentage of the activity remains at the injection site instead of circulating throughout the patient's body. This reduces the net available activity for uptake and changes the kinetics of uptake for subsequent imaging*(2-6)*.

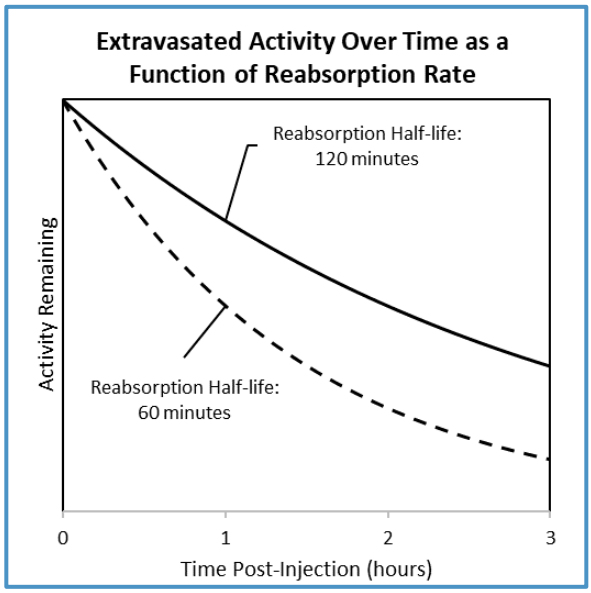

Figure 1. Representative graph of the way in which extravasated activity changes over time. Imaging time would typically occur at 1 hour post-injection.

Because diagnostic radiotracers are administered as a bolus, the extravasation can be modeled as an initial value that is reduced over time due to radioactive decay and biological reabsorption. For this work, we modeled reabsorption as a mono-exponential function. The time needed for resolution of the extravasated activity depends on the combination of radioactive and resorptive half-lives and the extravasation may or may not fully reabsorb by the time of imaging. Figure 1 depicts the way in which two hypothetical extravasations with differing reabsorption half-lives may resolve over time.

Clinical qualitative analysis of extravasations is not routinely done. However, it is possible to do so using single photon emission (SPECT) or positron emission tomography (PET) data. This creates a quantifiable snapshot of the extravasated activity at the time the image was acquired*(7)*. In order to quantify the overall significance of the extravasation throughout the uptake time and beyond, clinicians must know the rate of biological reabsorption.

There is technology (Lara®, Lucerno Dynamics LLC, Cary NC) which can monitor the injection site for excess radioactivity during and after the injection. These topical scintillation detectors generate time-activity curves (TACs) for both the injection and reference arms (Figure 2). TACs show the relative amount of local radioactivity over time.

In this investigation, we sought to understand the impact of a diagnostic radiotracer extravasation from the perspective of radiation safety and determine the amount of radiation dose likely to be deposited in tissue around the extravasation. Additionally, we investigated whether topical injection quality-control sensors could provide information about the rate of reabsorption for more accurate estimation of absorbed dose.

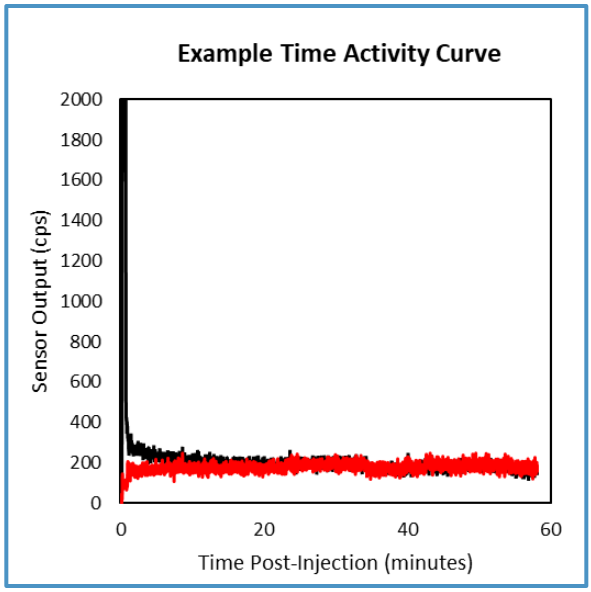

Figure 2. Example TAC graph generated from Lara® sensor data.

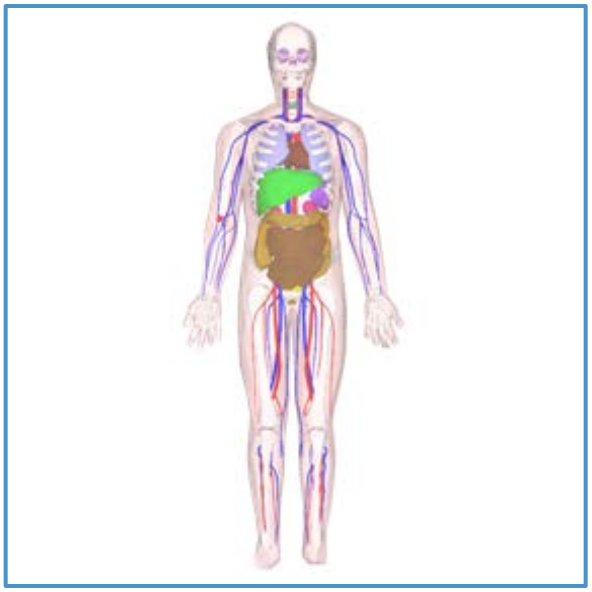

Figure 3. Example of the anthropomorphic model.

Methods

We used the GATE Monte Carlo framework* along with anthropomorphic 3D models † of a human (Figure 3) to simulate three extravasation scenarios.

The model was sized to represent an adult male with weight of approximately 69 kg. Internal organs were modeled using realistic material properties for tissue, bladder, brain, heart, intestines, kidneys, liver, lungs, skeleton and spleen. Throughout this analysis, extravasation activity at the time of imaging is used as a reference point, but total dose is calculated over the entire extravasation time based on the combined radioactive and biological reabsorption half-lives.

Where available, PET data was used to improve the simulation assumptions.

Table 1 details the activity, volume, and experimental basis for each simulated extravasation. Simulations of 1 second were run five times each and averaged. Each simulation was itself subdivided into 64 parts to assure randomness of the numerical particle generator. Equivalent dose was recorded in each organ as well as the extravasation site itself using 1 cm^3 voxels to calculate total organ doses in Sv/sec. In each example, total dose over time was calculated by integrating throughout the extravasation time period—defined as the time required for the extravasated dose to reach 5% of its initial value.

Simulation Identifier	Extravasation Activity at Imaging Time	Extravasation Volume	Reabsorption Half-life	Basis
A	4.5 mCi	5.5 cm^3	60 Minutes	Based on a clinical extravasation example with PET-measured SUV change.
B	0.11 mCi	2.0 cm^3	Based on Sensor TACs	Based on clinical extravasation examples with PET measurement of activity and volume. Reabsorption based on sensor TACs.
C	1 mCi	5 cm^3	60 Minutes	Hypothetical activity, volume, and reabsorption.

Table 1: Details of extravasation scenarios simulated.

* Geant4 Application for Emission Tomography. www.opengatecollaboration.org

† BodyParts 3D, ©2008 Life Science Integrated Database Center licensed by CC Display - Inheritance 2.1 Japan

Simulation A

Simulation A was based on a clinical example of ^{18}F-FDG extravasation that resulted in an approximately 50% reduction in tumor SUV relative to a non-extravasated repeat PET scan 5 days later. The injection site was outside of the PET field of view, so we made assumptions for extravasation shape (semi-planar volume located in dorsal hand) and volume (5.5 cm^3). The initial extravasated injection consisted of 13.72 mCi and PET imaging was performed 57 minutes post-injection. The repeat, non-extravasated injection was performed 5 days later and consisted of 14.5 mCi with PET imaging occurring 65 minutes post-injection. These parameters are within published guidelines for quantitative PET test-retest*(8,9)*. We can assume the tumor metabolism was unchanged*(10,11)* between the two PET scans.

According to compartment modeling of tumor glucose uptake, we know that the tumor uptake (SUV) at the time of imaging is related to the concentration of radiotracer in the blood throughout the uptake time*(12)*, referred to as the arterial input function (AIF):

$$\boldsymbol{SUV \approx AUC \times K_m + \overline{V}_r} \qquad [1]$$

Where $\boldsymbol{AUC}$ is the area under the AIF curve, $\boldsymbol{K_m}$ is the tumor's metabolic rate, and $\boldsymbol{\overline{V}_r}$ is the variability of the distribution volume. Because the two PET studies were only 3 days apart, $\boldsymbol{K_m}$ and $\boldsymbol{\overline{V}_r}$ are assumed to be constant. Thus, [1] becomes simply:

$$\boldsymbol{SUV \approx AUC} \qquad [2]$$

The $\boldsymbol{AUC}$ is the integral of the activity of ^{18}F-FDG in arterial blood. In the case of an ideal injection, it depends on initial activity as well as uptake into tissue and organs. In the case of an extravasated injection, however, reabsorption of the radiotracer over time dynamically alters the blood activity; it resembles a reduced height bolus followed by a slow infusion.

In order to calculate the change in SUV due to differences in the injection, Equation 2 becomes:

$$\frac{\boldsymbol{SUV_{ideal}}}{\boldsymbol{SUV_{extravasated}}} \approx \frac{\boldsymbol{AUC_{ideal}}}{\boldsymbol{AUC_{extravasated}}} \qquad [3]$$

Our overall methodology for Simulation A is based on linear system theory as described by Muzi et al.,

> *"PET tracers are assumed to behave in a linear, time-invariant fashion at the local tissue level, and can be described by an impulse response function." (14)*

When considering tissue uptake as a linear system, a bolus injection would be the impulse and the normal AIF curve would then be the impulse response. We used arterial blood sample data reported by de Geus-Oei, et al.*(13)* as a model of the normal AIF (Figure 4).

In the case of an extravasated injection, however, the AIF is a convolution of the normal impulse response with the altered input signal consisting of decreased initial impulse (bolus) followed by prolonged decaying exponential (reabsorption).

We used this approach along with an assumed reabsorption rate to determine the magnitude of an extravasation that would produce a 50% change in the SUV.

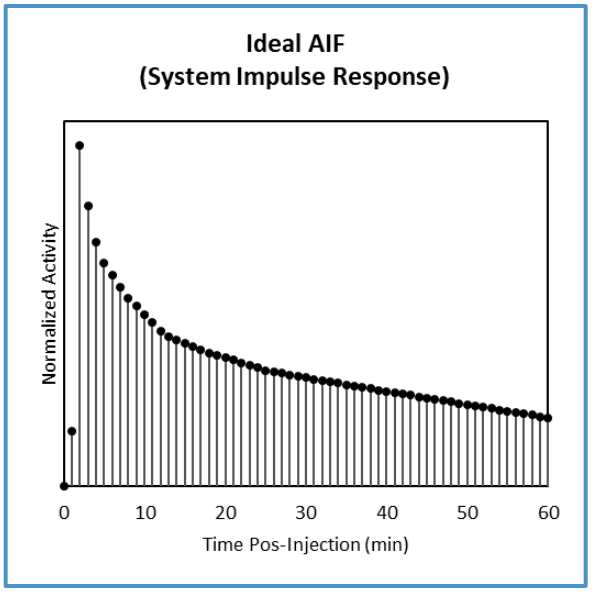

Figure 4. AIF curve for an ideal injection. This is the impulse response for the linear system.

Figure 5 shows the general form of the model for an altered input signal due to extravasation. It consists of the combination of a reduced height impulse followed by a decaying exponential signal due to reabsorption.

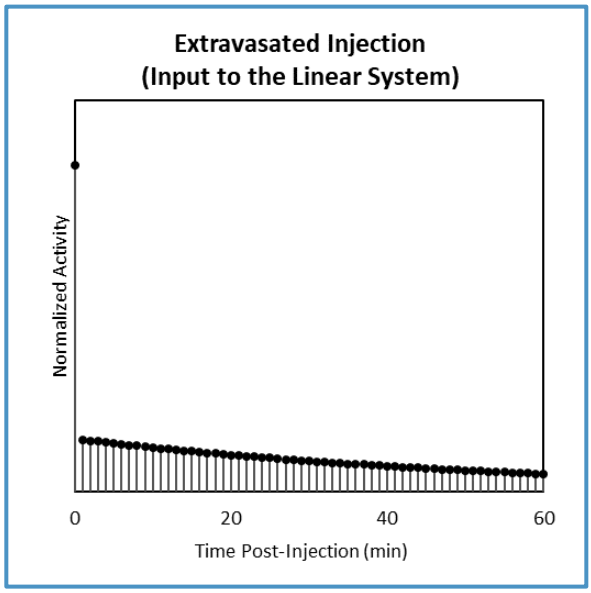

Figure 5. Example of the linear system input caused by an extravasation – impulse at time=0 followed by decaying exponential due to reabsorption.

This model can be used to describe the altered input for any extravasation given the initial extravasated activity and the reabsorption rate. To obtain the resulting blood concentration curve, we convolved this signal with the impulse response.

Finally, we used a least-squares approach to determine the specific extravasation magnitude that would result in a 50% reduction in SUV. Using a reabsorption rate with a 60-minute half-life, this magnitude was found to be 92% (Figure 6). The total injected activity of 13.72 mCi means the initial extravasation activity for Simulation A was 12.6 mCi.

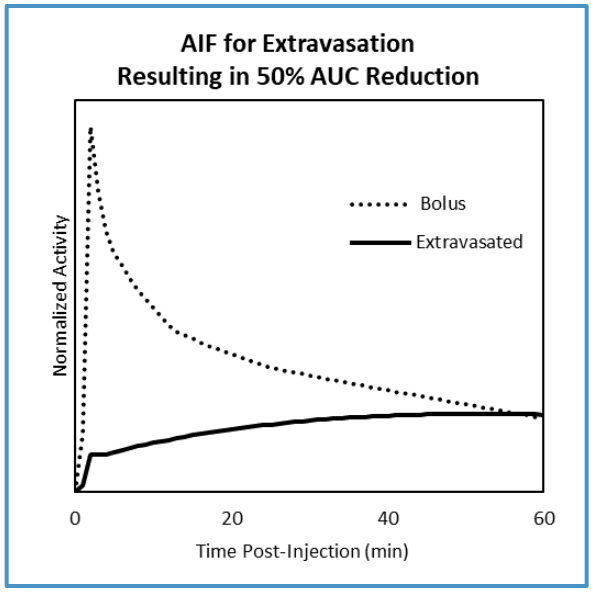

Figure 6. Comparison of AIF for an ideal bolus injection vs an extravasated injection. The resulting difference in AUC is 50%.

Simulation B

For simulation B, the extravasation volume (2.0 cm^3) and activity (0.11 mCi) both resulted from actual PET data measurements using regions of interest defined by isocontours with a threshold of 30% of SUV_{max}.

Additionally, topical injection quality-control sensors data was used as a measure of radiation near the injection site. Whereas the rate of reabsorption was assumed in Simulation A, we used the sensor TAC data to estimate the relative rate of reabsorption in Simulation B.

Sensor TAC data from the reference arm was subtracted from the injection arm data to remove "background" counts from the patient's torso. After the time of sensor removal (81 minutes post-injection), an exponential fit of the last 30 minutes of TAC data was used to extrapolate to 5% of the initial TAC value. Figure 7 shows the TAC data with extrapolation.

For the rate of reabsorption, we used the actual TAC data for the time period available, and then the extrapolation.

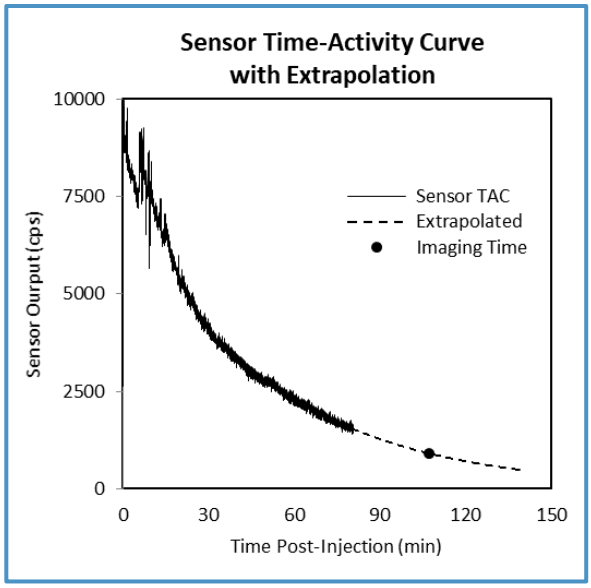

Figure 7. Sensor time-activity curve for Simulation B. with extrapolation after the sensors were removed.

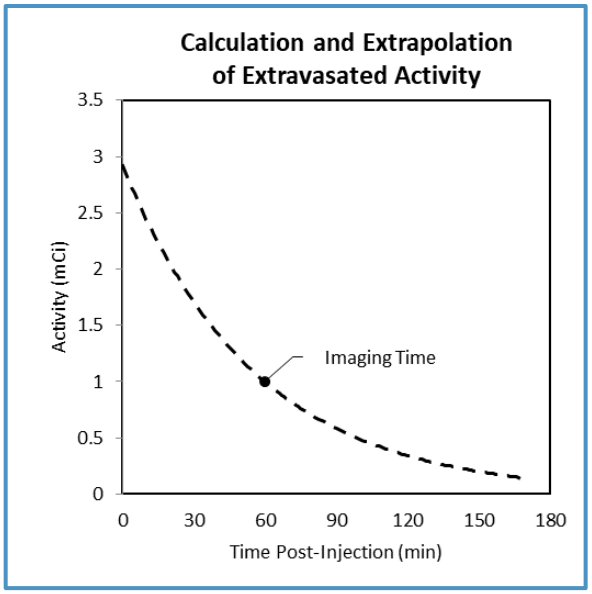

Figure 8. Graph showing calculation of extravasation activity for Simulation C using hypothetical imaging time activity and reabsorption rate.

Simulation C

Simulation C further demonstrates the general concepts with a hypothetical extravasation of ^{18}F-FDG resulting in 1 mCi remaining within a 5 cm^3 sphere at the imaging time of 60 minutes post-injection. This simulation used a reabsorption half-life of 60 minutes. Figure 8 shows the extravasation activity to the point where it is 5% of its initial value. In order to result in 1 mCi within the extravasation at the imaging time of 60 minutes, the initial activity was approximately 2.9 mCi.

Results

Analysis of the voxelized dose phantom models showed that although most of the body registered non-zero dose, none of the scenarios resulted in significant dose to organs or tissue other than the extravasation tissue. Thus, analysis will focus on radioactive dose to the tissues affected by the extravasation volumes only.

Simulation A

Figure 9 shows the simulation geometry with extravasation volume identified by the yellow arrow. Figure 10 shows equivalent dose over the entire extravasation time period. Using a reabsorption half-life of 60 minutes, the 12.6 mCi extravasation resulted in dose being deposited for 166 minutes resulting in a total equivalent dose of 11.5 Sv to the 5.5 cm^3 of infiltrated tissue.

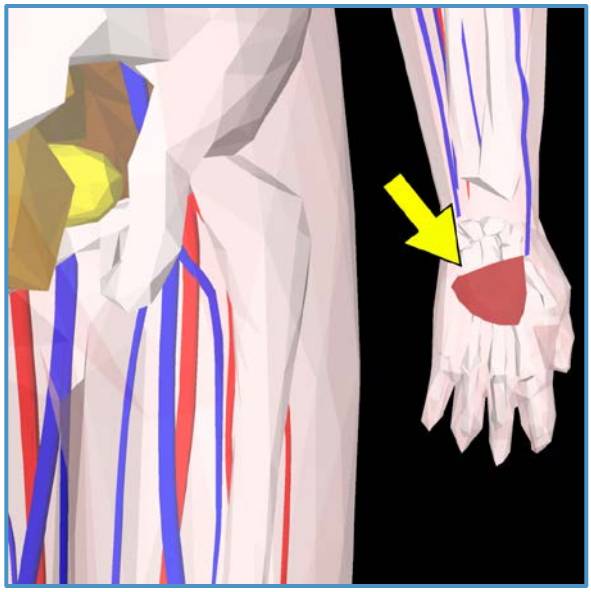

Figure 9. Geometry for Simulation A with extravasation volume identified.

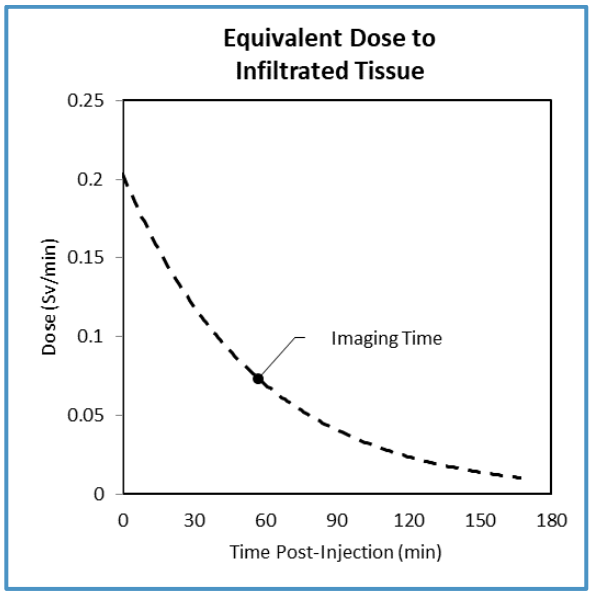

Figure 10. Dose to the infiltrated tissue in Simulation A over time. Total dose over 166 minutes was 11.5 Sv.

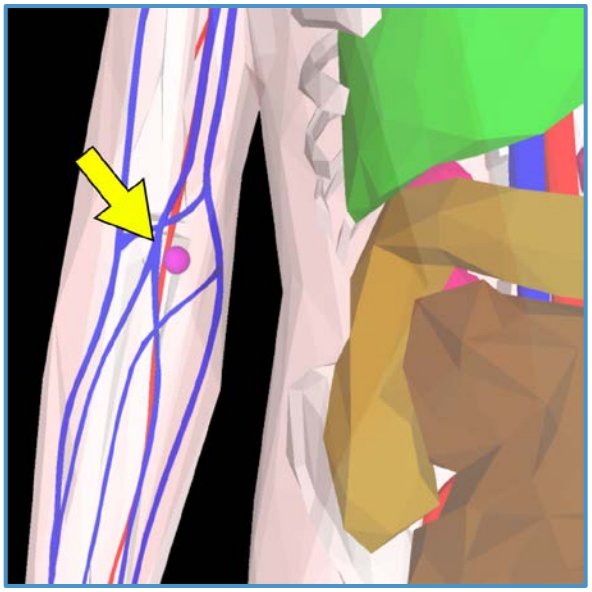

Figure 11. Geometry for Simulation B with extravasation volume identified.

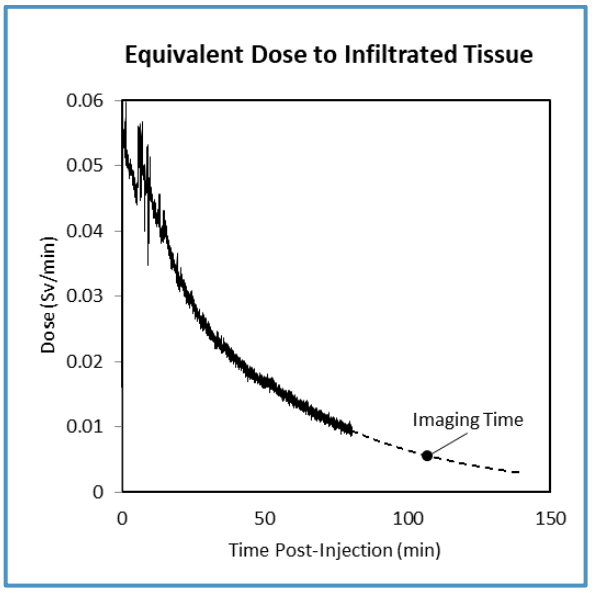

Figure 12. Dose to the infiltrated tissue in Simulation B over time. Total dose over 139 minutes was 2.26 Sv.

Simulation B

Figure 11 shows the simulation geometry with extravasation volume identified by the yellow arrow. Using an exponential fit (R^2=0.96) to extrapolate from the last 30 minutes of sensor TAC data, the 0.11 mCi extravasation resulted in dose being deposited for 139 minutes resulting in a total equivalent dose of 2.26 Sv to the 2 cm^3 of infiltrated tissue (Figure 12).

Simulation C

Figure 13 shows the simulation geometry with extravasation volume identified by the yellow arrow. Using a reabsorption half-life of 60 minutes, the 1 mCi extravasation resulted in dose being deposited for 166 minutes resulting in a total equivalent dose of 3.41 Sv to the 5 cm^3 of infiltrated tissue (Figure 14).

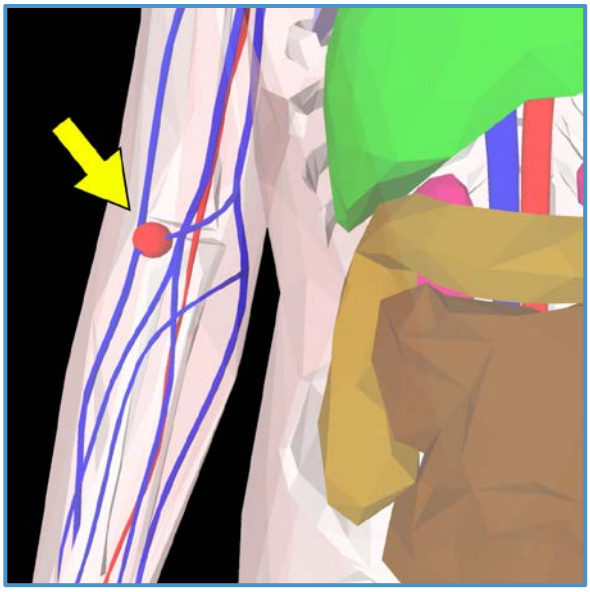

Figure 13. Simulation geometry for Simulation C with extravasation volume identified.

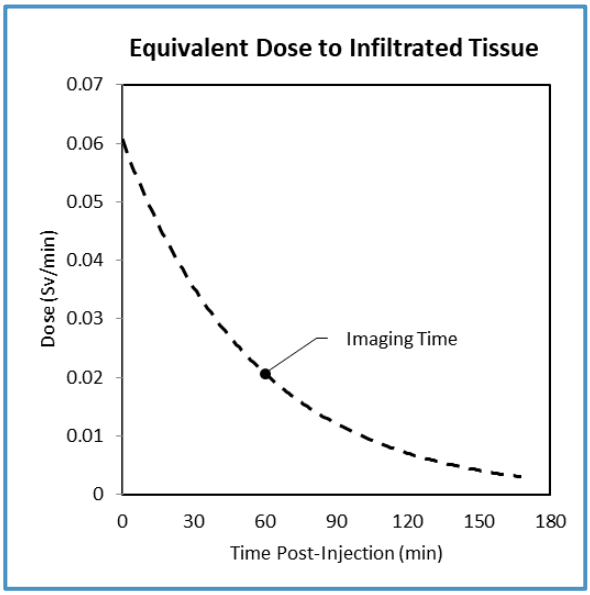

Figure 14. Dose to the extravasated tissue in Simulation C over time. Total dose over 166 minutes was 3.41 Sv.

Table 2 details the results of all three simulations in terms of total extravasation time and total equivalent dose to the tissue.

Discussion

In this work, we investigated three extravasation scenarios. Note that in these simulations, no activity was modeled in the rest of the body—only the activity within the extravasation. This means that all dose calculated is due to the extravasation itself.

In calculation of absorbed dose over time, it is important to understand the ways in which the extravasation changes. Shapiro, Pillay and Cox reported a method to estimate worst-case dose*(15)* by assuming no reabsorption. While this would produce an estimate, we feel it will be unrealistically high in most cases. For instance, if Simulation C were assumed to have no or very slow reabsorption, the resulting dose could be multiple times what it should be because all the radiotracer decays in situ. This impact is even more pronounced with longer-lived isotopes.

While we found no reports of measured reabsorption rate for extravasations of ^{18}F-FDG, there are mathematical bounds for specific situations. We tested our assumptions for Simulation A by calculating the extravasation magnitude required as a function of reabsorption rate. In order to result in a 50% change in SUV, the reabsorption half-life cannot be less than approximately 32 minutes as this would require an initial extravasation of greater than 100%. Likewise, as reabsorption rate increases, the extravasation magnitude required to result in an SUV reduction of 50% asymptotically approaches 50% (Figure 15).

Simulation Identifier	Imaging Time	Extravasation Activity at Imaging Time	Total Extravasation Time	Total Equivalent Dose
A	57 minutes	4.55 mCi	166 minutes	11.5 Sv
B	107 minutes	0.11 mCi	139 minutes	2.26 Sv
C	60 minutes	1.00 mCi	166 minutes	3.41 Sv

Table 2: Summary of simulation parameters and results.

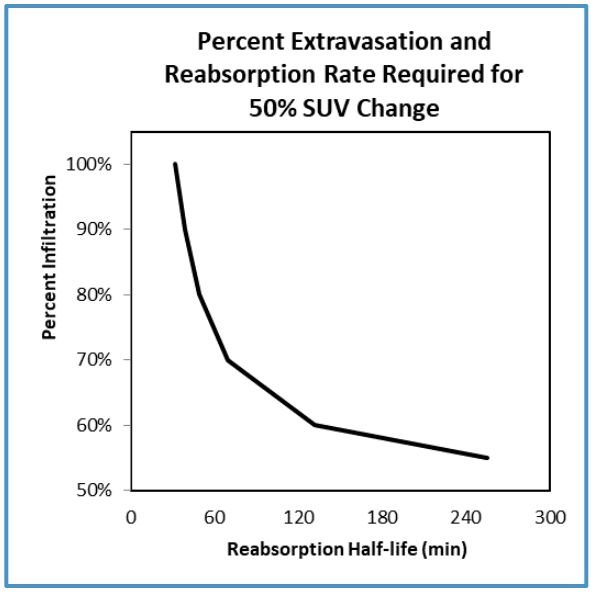

Figure 15. Relationship between percent extravasation and reabsorption rate that are required to result in a 50% change in SUV.

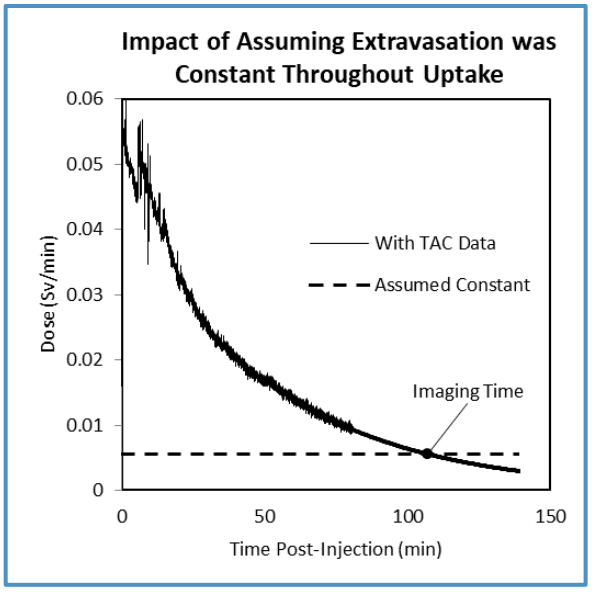

Figure 16. The difference between using sensor TAC data to estimate reabsorption vs assuming the extravasated activity was constant throughout.

For Simulation A, we used a nominal reabsorption rate in order to demonstrate the possible impact in terms of radiation dose. However, depending on reabsorption rate, results could be between 10 and 17 Sv.

Simulation B is interesting in that the extravasation was relatively small in both size and activity at the time of imaging. Simulation parameters were based on PET measurements, but imaging provided no information about the uptake period or reabsorption rate. We used sensor TAC data for a proxy of the reabsorption rate. Without access to the sensor TAC data, the reabsorption rate would have to be assumed.

We calculated the possible error due to assumption of reabsorption rate for Simulation B and found that rates between 20-70 minutes would be off by as much as a factor of 3 when compared to the sensor TAC results.

On the other hand, one might assume that the extravasated dose present at the time of imaging was constant throughout the uptake time. In the case of Simulation B, the dose estimate would be too low by a factor of 3 (Figure 16).

Assumption of the reabsorption rate is not enough to accurately quantify the dose. Repeated PET or SPECT imaging of the extravasation could be used*(7)*, but would increase imaging workload and cost.

We propose that injections be monitored using topical sensors and in the case of suspected extravasations, the injection site should be imaged. Together, image-based measurements of the extravasation activity along with time-activity curve data from topical sensors can be used to estimate radiotracer activity present over time and the deposited dose.

Conclusion

As demonstrated in this work, even extravasations that appear negligible on PET could be significantly worse throughout the uptake time. Imaging alone cannot be used for assessment of extravasated dose. Rather, it is important to know the time course over which the activity is reabsorbed during the uptake time—including after imaging time. We found no reports of soft-tissue injury due to diagnostic radiotracer extravasation, but as van der Pol et. al report*(16)*, cases could be underreported.

As discussed by Hoop*(17)*, the identification and mitigation of radiopharmaceutical extravasations must begin with monitoring the site immediately after injection. Prompt identification allows immediate implementation of harm mitigations*(16)*, but continued monitoring with topical sensors throughout the uptake period can be used to estimate the rate of reabsorption and equivalent dose.

In conclusion, diagnostic radiopharmaceutical extravasations can exceed 10 CFR Part 35 Subpart M Reporting and Notification criteria and have the potential to cause harm.

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Appendix B: Impact of Lutetium-177 Theranostic Infusion Extravasation—a Monte Carlo Investigation

Background

Paravenous extravasation of radio-pharmaceutical agents is not rare*(1-7)*. Hung et al.*(7)* report that:

> With infiltrated activity, the intended route of radiopharmaceutical administration usually is intravenous injection, and there is either a partial or complete extravasation of the intended dose. The possible consequences of an infiltrated radiopharmaceutical injection are not only misinterpretation (if the infiltration site is not identified) of the study or loss of diagnostic information or therapeutic value (if complete extravasation occurs), but also an unanticipated local absorbed radiation dose to the patient with other potential complications, such as local hematoma, phlebitis, phlebothrombosis, or sepsis.

While diagnostic radiopharmaceutical injections typically consist of 1 to 20 mCi*(7)*, *radiotherapeutic* administrations can be hundreds of mCi. Furthermore, radiotherapeutic agents typically emit beta radiation and have relatively long half-lives resulting in further increased risk of local radiation dose in the event of an extravasation.

In the case of suspected *radiotherapeutic* extravasation Van der Pol et al.*(8)* point out that several experts advocate mitigations such as elevation, hyperthermia, and massage. The goal of such actions would be timely dispersal the locally concentrated activity. However, mitigation requires knowledge or suspicion of an extravasation event. Several papers report cases of extravasation where the patient felt no pain and there was no immediate suspicion of extravasation*(9-11)*.

> At the conclusion of the injection, the patient volunteered that the injection had been the least painful i.v. entry he had experienced. Seven days later, imaging failed to detect any radioactivity in the field of view centered on the adrenal glands. Monitoring of the injection site demonstrated essentially complete retention of the radiopharmaceutical at the site*(11)*.

In the case of an unrecognized extravasation, the locally concentrated activity will disperse over time through lymphatic pathways. The rate of dispersal depends on the nature of the extravasation as well as the radiopharmaceutical itself. For instance, ^{131}I-Iodocholesterol is relatively insoluble in water*(11)* and will remain immobile in the interstitial space longer than 18F-FDG which is water soluble[†].

LUTATHERA [‡] (lutetium Lu-177 dotatate) is a prescription medicine using hormone receptor somatostatin to treat adults with a cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Infusions consist of 200 mCi with a volume of 20 mL administered intravenously over the course of 30 to 40 minutes diluted using a saline drip carrier. Prescribing information [§] describes administration instructions as:

> Insert a 2.5 cm, 20-gauge needle (short needle) into the LUTATHERA vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport LUTATHERA during the infusion). Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the LUTATHERA vial prior to the initiation of the LUTATHERA infusion and

[†] Safety Data Sheet, Fluorodeoxyglucose-F18, Lantheus Medical, accessed Feb 5, 2019 http://www.lantheus.com/assets/fluorodeoxyglucose-f18_oct13-2015-2-1.pdf

[‡] LUTATHERA® is a registered trademark of Advanced Accelerator Applications SA

[§] LUTATHERA Prescribing Information, accessed Feb 5, 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf

> do not inject LUTATHERA directly into the sodium chloride solution.
>
> Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the LUTATHERA infusion into the patient.
>
> Use a clamp or pump to regulate the flow of the sodium chloride solution via the short needle into the LUTATHERA vial at a rate of 50 mL/hour to 100 mL/hour for 5 to 10 minutes and then 200 mL/hour to 300 mL/hour for an additional 25 to 30 minutes (the sodium chloride solution entering the vial through the short needle will carry the LUTATHERA from the vial to the patient via the catheter connected to the long needle over a total duration of 30 to 40 minutes).

LUTATHERA emits both beta and gamma radiation. Extravasation during an infusion of LUTATHERA would not only prevent systemic administration of the agent but would expose the patient's arm tissue to potentially high levels of radiation. This exposure could cause radiation damage to the tissue which might take days*(11)*, months*(9)*, or even years*(7)* to become evident.

Pharmacokinetics are defined as the study of the time course of drug absorption, distribution, metabolism, and excretion*(12)*. According to the prescribing information for LUTATHERA, its pharmacokinetics are:

> Within 4 hours after administration, lutetium Lu-177 dotatate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid.
>
> The mean clearance is 4.5 L/h for lutetium Lu-177 dotatate. The mean effective blood elimination half-life is 3.5 hours and the mean terminal blood half-life is 71 hours.
>
> Lutetium Lu-177 dotatate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following LUTATHERA administration. Prolonged elimination of lutetium Lu-177 dotatate in the urine is expected; however, based on the half-life of lutetium-177 and terminal half-life of lutetium Lu-177 dotatate, greater than 99% will be eliminated within 14 days after administration of LUTATHERA.

No information was found in literature describing the pharmacokinetics or reabsorption of LUTATHERA with respect to tissue extravasation. However, based on the mean effective blood elimination half-life of 3.5 hours, we assume that the rate of reabsorption for extravasated tissue would be 1 to 8 hours.

The prescribing information also describes measures to be taken in the case of extravasation:

> The infusion of the medicinal product must be immediately ceased and the administration device (catheter, etc.) removed. The nuclear medicine physician and the radio-pharmacist should be informed. All the administration device materials should be kept in order to measure the residual radioactivity and the activity actually administered and eventually the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.
>
> To continue LUTATHERA® infusion, it is mandatory to use a new catheter possibly placing it in a contralateral venous access. No additional medicinal product can be administered to the same side where the extravasation occurred.
>
> In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, aspiration of extravasation fluid, sodium chloride 9 mg/ mL (0.9%) solution for injection flush injection or applying warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

We are aware of LUTATHERA extravasation from FDA approval information, from one LUTATHERA center, and also from published literature. Tylski et al. report on an extravasation resulting in estimated dose to the arm of 2.8-7.8 Sieverts (Sv)*(13)*. In this case, warming and repeated massage of the injection site were used as mitigations.

The objective of our work reported here was to use Monte Carlo simulation to investigate the impact of a LUTATHERA extravasation in terms of localized radiation exposure, radiation exposure to the adjacent skin, and loss of systemic availability of the radiotherapeutic agent.

Methods

We developed an anthropomorphic model representing a 68 kg adult man. Tissue and organs were modelled accurately using geometry files from the BodyParts3D[**] database. Figure 1 shows the arm portion of the human model used for Monte Carlo analysis.

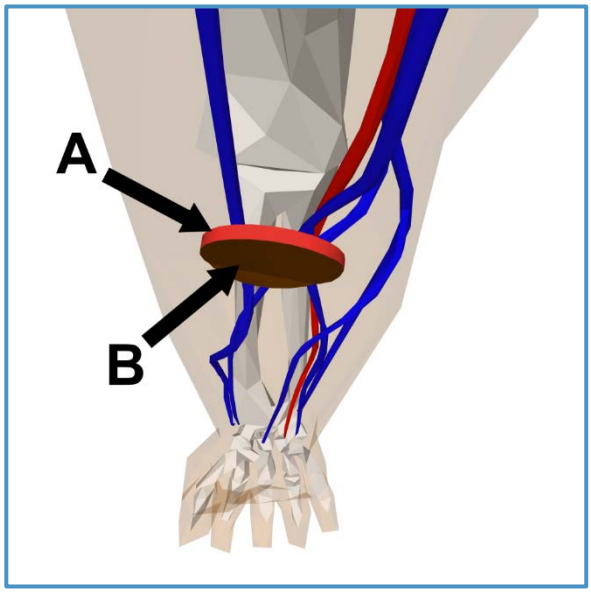

Figure 1. Anthropomorphic model used in simulations. The red disc (A) is the extravasation volume. The brown side (B) represents the skin volume.

For the extravasation volume, we modeled a cylinder within the antecubital fossa with thickness 3.93 mm and total volume of 5 cm^3. The skin was modeled as the circular area directly adjacent to the cylinder with thickness 0.07 mm[††]. Activity was added only to this extravasation volume and all dose calculated in this work is due to the hypothetical extravasation only.

Using administration guidelines provided for LUTATHERA, we calculated the total infusion volume to be 100 mL. In this case, a 5% extravasation would result in 5 mL containing 10 mCi within the arm tissue. The GATE [‡‡] Monte Carlo simulation framework was used to calculate equivalent radioactive dose to the antecubital fossa tissue. This result, in Sv/sec/mCi, was then used to calculate dose throughout the time of infusion.

We calculated the infusion activity over time by applying dilution formulae to the combination of saline and LUTATHERA throughout the infusion time. Figure 2 depicts the activity being infused during the procedure according to the administration guidelines for LUTATHERA. Radioactive decay (half-life = 6.647 days[§§]) is applied to all calculations. After 30 minutes, 2.9 mCi are left in the vial (1.5% of total) which would be infused through manual flushing.

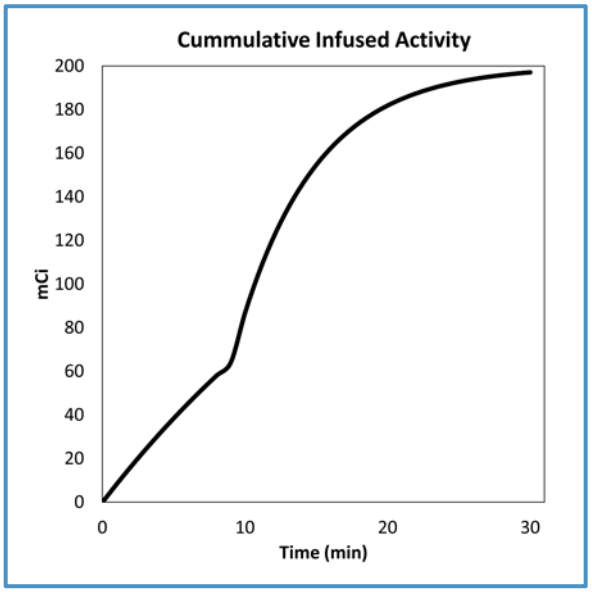

Figure 2. Graph of infused activity over time.

Re-absorption of the extravasation activity would cause the sequestered activity to enter systemic circulation over time. The exact rate of reabsorption is unknown but was modeled using a mono-exponential function with half-lives of 1, 2, 4, and 8 hours. The true reabsorption function likely depends on the nature of the extravasation as well as patient-specific factors.

Using the amount of LUTATHERA that decayed while sequestered within the arm tissue, we calculated the reduced therapeutic availability due to the extravasation.

Finally, dose to the skin was calculated using the modeled skin volume data.

[**] BodyParts 3D, Copyright 2008 Life Science Integrated Database Center licensed by CC Display - Inheritance 2.1 Japan

[††] United States Nuclear Regulatory Commission, Glossary, Shallow Dose Equivalent, https://www.nrc.gov/reading-rm/basic-ref/glossary/shallow-dose-equivalent-sde.html

[‡‡] Geant4 Application for Emission Tomography. www.opengatecollaboration.org

[§§] IAEA - Nuclear Data Section, accessed Feb 5, 2019, https://www-nds.iaea.org/

Results

Figure 3 shows the activity within the extravasation for each reabsorption half-life tested. Plotted data continues until the extravasation activity falls to 5% of its maximal value.

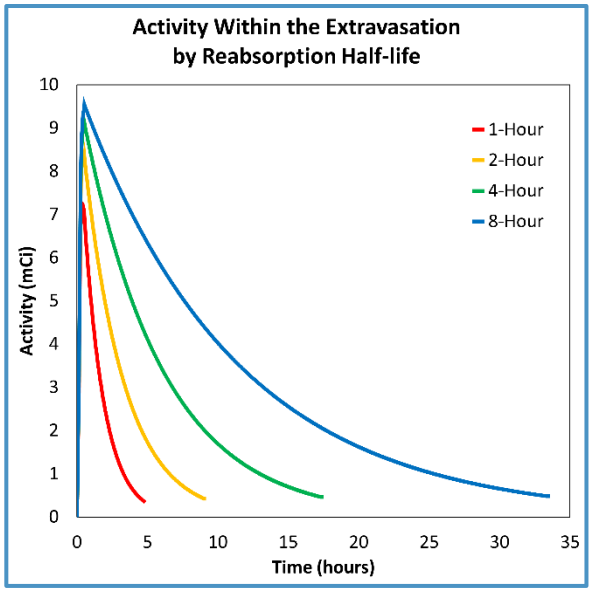

Figure 3. Graph of extravasation activity over time as a function of reabsorption half-life for a 5% extravasation.

Using this information along with the results of the Monte Carlo simulation for extravasation tissue dose (1.76E-04 Sv/sec/mCi), we calculated equivalent dose to the antecubital fossa tissue over time. Figure 4 shows this cumulative dose in Sv for each of the reabsorption half-lives.

Given the results of cumulative dose to the tissue, we can determine the amount of LUTATHERA that did not make it into systemic circulation as it should have. Based on the tissue doses calculated, the amount of LUTATHERA that decays in the arm and fails to fulfill its intended purpose is between 1.27% and 1.54% (Table 1).

Dose to the skin was calculated for each reabsorption half-life and was found to be between 2.6 and 22 Sv.

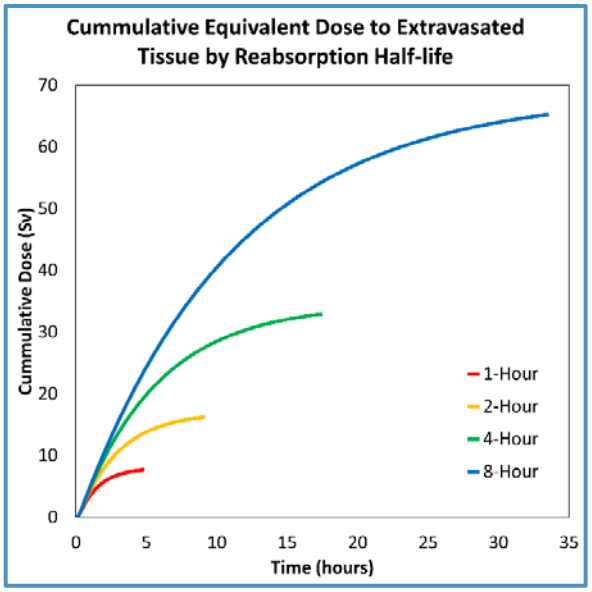

Figure 4. Graph of cumulative dose to the extravasated tissue as a function of reabsorption half-life.

Discussion

In this work, we first determined both the systemic and extravasated activity portions of an infusion of LUTATHERA with failed intravenous access. We assumed 5% of the infusion would be extravasated and then reabsorbed. Based on assumptions of the rate of this reabsorption, we calculated total equivalent dose to the extravasation site as well as the impact to the intended LUTATHERA therapeutic administration.

While we found that this 5% extravasation would only reduce the intended therapeutic LUTATHERA administration by 2-3%, the equivalent dose to arm tissue and skin could be severe (2-22 Sv Skin, 7-65 Sv Tissue) depending on reabsorption rate.

Tylski et al.*(13)* report a case of Lutetium-177 extravasation where they performed serial imaging of the injection site. In this example, they suspected extravasation and implemented warming and massage of the area as mitigation. With these mitigations, reabsorption half-life was estimated as

Reabsorption Half-life (hours)	Total Tissue Dose (Sv)	Total Skin Dose (Sv)	Reduced Therapeutic Availability (mCi)	Reduced Therapeutic Availability (%)
1	7.68	2.61	2.55	1.27%
2	16.19	5.50	2.82	1.41%
4	32.91	11.18	2.99	1.49%
8	65.21	22.15	3.08	1.54%

Table 1: Total extravasation dose, skin dose, and reduced therapeutic effectiveness as a function of reabsorption half-life.

3.5 hours. Although this was the only report of Lu-177 extravasation we found, it does grossly affirm our assumptions of reabsorption half-life. It is likely that the nature of an extravasation would impact its reabsorption rate along with patient-specific factors such as lymphatic health.

We made assumptions about the size and shape of the extravasation. Many factors could change the absorbed dose in specific cases. Because the mean penetration depth of beta radiation from Lu-177 is 0.67 mm*(14)*, skin dose is heavily dependent on where the extravasated activity resides. Likewise, the local concentration of the activity determines the dose to arm tissue.

Conclusion

In this work, we investigated a simulated LUTATHERA extravasation of 5%, which may go unnoticed during the infusion process. In this example, only 2-3% of the total radiopharmaceutical administration will decay while sequestered in the arm. The remaining activity is distributed systemically through reabsorption over time. Modeling the equivalent radiation dose for several reabsorption rates, we determined that significant dose could be absorbed by not only the skin, but the tissue itself.

For suspected radiopharmaceutical extravasations in general, several authors recommend implementation of mitigation measures*(9,10,15-20)* as well as repeated measurement of the injection site activity*(10,11)* to provide information on mitigation effectiveness and reabsorption rate. However, given the possible severity of radiotherapeutic extravasation and the difficulty in identification during the infusion, we suggest that a real-time feedback mechanism is needed. Feedback about the injection site activity during the infusion would allow cessation of a suspected extravasation and immediate implementation of mitigations according to the radiopharmaceutical prescribing information.

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Appendix C: Suggested Injection-Monitoring Procedure

To maximize patient safety, use the following method:

- Injections shall be monitored by localized gamma ray detectors during the uptake period for presence of extravasation.
- If extravasation is detected or suspected, the injection site shall be included in the imaging FOV during the imaging procedure.
- Images of the injection site shall be reviewed and quantitative measurements of the extravasation activity and volume shall be calculated.
- Estimates of effective dose equivalent to the tissue shall be calculated by assuming the activity was constant throughout the uptake time.
    - If the constant-activity dose estimate is greater than the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.
    - If the constant-activity dose estimate is less than the 0.5 Sv limit, the dynamic nature of the activity over the uptake time must also be considered. Estimate the dynamic-activity dose to the extravasated tissue by combining the measured extravasation activity and volume with the detector data. Detector data informs this estimate by representing the dynamic nature of the activity throughout the uptake time, and shall be used to extrapolate to a nominal level of exposure. If this dynamic-activity dose estimate exceeds the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.

Alternate method. If gamma ray detectors are not used, then injection sites should be routinely included in the imaging FOV in order to detect extravasation.

- If extravasation is detected on the scan images, injection site image data shall be reviewed and quantitative measurements of the extravasation activity and volume shall be calculated.
- Estimates of effective dose equivalent to the tissue shall be calculated by assuming the activity was constant throughout the uptake time.
    - If the constant-activity dose estimate is greater than the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.
    - If the constant-activity dose estimate is less than the 0.5 Sv limit, dynamic activity changes shall be estimated based on historical time-activity curve characterizations from literature. Estimate the dynamic-activity dose to the extravasated tissue by combining the measured extravasation activity and volume with the historical time-activity curve characterization. Historical data informs this estimate by approximating the dynamic nature of the activity throughout the uptake time, and shall be used to extrapolate to a nominal level of exposure. If this dynamic-activity dose estimate exceeds the 0.5 Sv limit, the extravasation shall be reported as a medical event to the NRC as well as to treating physicians and patients to ensure that the extravasation does not impact patient care.

Monitoring injections for extravasation will result in a better understanding of the real rate of nuclear medicine extravasations and motivate improvement efforts that lead to better injection processes. These efforts will lead to fewer extravasations, less unintended radiation exposure to tissue, and higher-quality images used to help guide patient care.