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October 9, 2019

Michael Layton, Director
Division of Materials, Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards
Nuclear Regulatory Commission

Dear Michael,

I am writing you to ask the Nuclear Regulatory Commission (NRC) to reject a September 10, 2019 Advisory Committee on the Medical Use of Isotopes (ACMUI) recommendation concerning nuclear medicine injection extravasations. Through conversations with Andrea Kock, I am aware that you are just starting your new role with the medical group. So, before detailing my specific request, I am including some contextual information that you may find useful.

Background

In 1980, the NRC established a policy that exempted nuclear medicine injections extravasations from misadministration reporting. The policy was based on the assumption that extravasations were a frequent occurrence during intravenous and intraarterial injections and were "virtually impossible to avoid". In 2008, the NRC – spurred by an 18F-FDG extravasation medical event report, the increased clinical use of positron-emitting diagnostic radiopharmaceuticals, and the introduction of new high-activity beta- and alpha-emitting therapeutics – asked the ACMUI if the 28 year-old extravasation policy was still appropriate. In December 2008, the ACMUI recommended that the NRC retain the 1980 reporting exemption policy for diagnostic radiopharmaceuticals. In May 2009, the ACMUI recommended to retain the exemption policy for radiotherapeutic extravasations, as well.

On December 11, 2018, Lucerno met with NRC staff to share recent evidence that nuclear medicine injection extravasations are not virtually impossible to avoid. The staff recommended Lucerno present this data during the Spring 2019 ACMUI meeting. On April 2, Lucerno sent a written request with supporting evidence to the NRC (Chair Svinicki and Ms. Andrea Kock) requesting that the NRC and the ACMUI re-evaluate the 1980 decision regarding extravasations and begin requiring medical event reporting of radiopharmaceutical extravasations that exceed Subpart M reporting limits. On April 3, Lucerno presented findings regarding nuclear medicine extravasations to the ACMUI. At the end of the presentation, the Chair of the ACMUI formed a subcommittee and asked them to evaluate the 1980 decision that exempted extravasations from misadministration, and then later, medical event reporting.

From April through September 2019, leaders in nuclear medicine, patients and other interested parties sent letters to the NRC, the ACMUI Chairman, and the ACMUI subcommittee requesting that the subcommittee recommend that extravasations that meet reporting criteria be reported to the NRC. During this same period, Lucerno provided the NRC, the ACMUI Chairman, and the subcommittee a copy of a publication which demonstrated that extravasation rates could be significantly improved and two examples of recent patient cases where diagnostic extravasations resulted in dose to patient tissue that exceeded NRC reporting limits.

On September 10, 2019, the subcommittee shared their recommendations with the ACMUI. The subcommittee continued to support retaining the 1980 exemption policy. Furthermore, they recommended that extravasations should not be regulated by the NRC and that these injection

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issues should be considered the result of patient intervention. One subcommittee member expressed a dissenting opinion and recommended that extravasations that exceed NRC reporting limits be reportable. The ACMUI accepted the subcommittee's majority recommendations.

Request

The NRC should reject the ACMUI September 10, 2019 recommendations regarding extravasations for the following two reasons:

1. The ACMUI subcommittee did not reconcile its recommendations with new evidence that invalidates the 1980 assumptions–assumptions which led to the current NRC policy that exempts extravasations from misadministration/medical event reporting. In particular, there is no indication the subcommittee considered the submitted evidence that extravasations are no longer virtually impossible to avoid.
2. Much of the information that the subcommittee shared with the ACMUI and NRC was inaccurate or incomplete, as shown in the following table. Sections referenced in the table are part of the document accompanying this letter.

Subcommittee statement/recommendation	Status
There is no evidence at this time to recommend a change in policy	**Inaccurate** – there is clear, peer-reviewed, evidence. Please see the section titled **Extravasations Can Be Avoided.**
Members unaware of any cases of documented patient harm due to extravasations	**Inaccurate** – the FDA adverse event and European vigilance reporting databases shows 55 cases of documented patient harm. There are over 50 peer-reviewed papers that indicate how patients have been or can be harmed by diagnostic as well as therapeutic extravasations. Please see the section titled **Documented Patient Harm.**
The NRC should classify extravasations as patient intervention	**Inaccurate** – extravasations, as discussed by the ACMUI in 2008 and 2009 and supported by a recently published peer-review article, are not a patient intervention issue. Extravasations are primarily the result of technologist, technique, and equipment issues. Please see the section titled **Authorized User Responsibility, Not Patient Responsibility.**
Extravasation is a practice of medicine issue and should not be regulated by NRC	**Inaccurate** – the Commission has been consistent in their policy which considers the improper administration of radiopharmaceuticals to be a regulatory concern. Additionally, the Commission does not consider equipment, qualifications of paramedical personnel, or reporting of misadministrations to be exclusively the practice of medicine. The ACMUI position is also inconsistent with recommended practices from the International Atomic Energy Agency (IAEA). Please see the section titled **NRC Jurisdiction.**
Clinical aspects of extravasations have been discussed by ACMUI in 2008 and 2009 and ACMUI did not recommend changing NRC policy	**Incomplete and likely inaccurate** – based on a review of the transcripts of these meetings, the 2008/2009 discussions focused on professional aspects, rather than patient clinical implications, of extravasations. Please see the section titled **Previous ACMUI Recommendations to Retain Exemption Not Based on Clinical Aspects.**
Medical event is defined as a discrepancy of a total dosage of +/- 20% delivered dose	**Inaccurate** – the definition of medical event is broader than the quoted text shared with the ACMUI and includes unintentional exposure to the patient. Please see the section titled **Extravasations Can Meet Medical Event Reporting Criteria.**

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Subcommittee statement/recommendation	Status
Technology presented to the ACMUI is for PET radiopharmaceuticals only None of the total doses in the extravasations of non-FDG isotopes meet the NRC's medical event criteria	**Inaccurate** – the presented technology is applicable to all radiopharmaceuticals. The FDA adverse event and European vigilance reporting databases lists both PET and SPECT radiopharmaceuticals that have caused serious adverse events due to extravasations. It is likely these SPECT extravasations would exceed NRC reporting criteria. Furthermore, we are including examples in the accompanying documentation showing that extravasation of Tc-99m radiopharmaceuticals may have exceeded reporting criteria. Please see the section titled **Both PET and SPECT Extravasations Can Meet Medical Event Reporting Criteria.**
SUV not relied on solely	**Incomplete** – the subcommittee did not consider the American College of Radiology quality measure or additional information provided to the subcommittee over the past several months. Please see the section titled **Quantification Matters.**
Minority Opinion – Extravasations that exceed the subpart M reporting criteria should be reported – to exclude extravasations is inconsistent with other regulations and is unwarranted	**Accurate** – please see the section titled **Dissenting Opinion.**

Based on the table above, we conclude the ACMUI and the subcommittee have made an erroneous decision regarding this extravasation issue. Therefore, I respectfully request that the NRC consider our submitted evidence and reject the ACMUI's recommendation.

In the accompanying documentation, please find further detail to support my request.

Thank you for your thoughtful consideration on this matter.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ron Lattanze
Chief Executive Officer

Enclosure: NRC Request Supporting Information

cc:
Andrea Kock
Chris Einberg
Lisa Dimmick
Said Daibes
Kellee Jamerson

NRC Request Supporting Information

October 9, 2019

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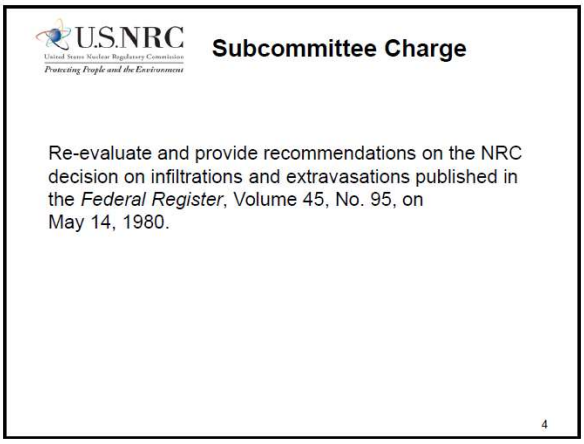
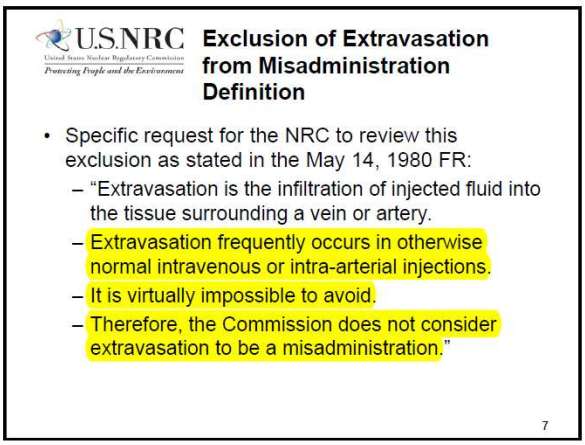
Supporting Information

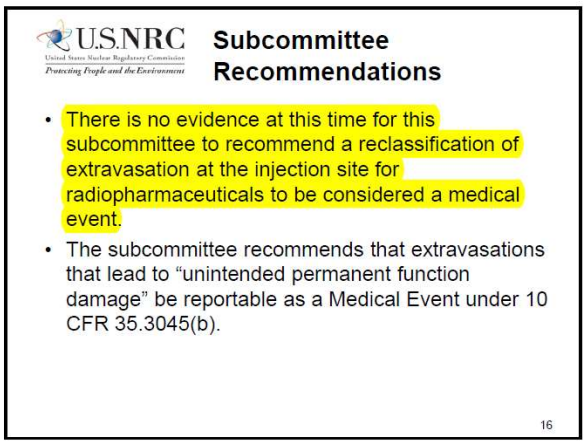
Lucerno is providing the NRC a review of the subcommittee presentation with additional information to support the request to reject the ACMUI recommendations and to highlight discrepancies in the information provided by the subcommittee.

A. Extravasations Can Be Avoided

The subcommittee was charged with reviewing the 1980 policy that exempted extravasations from being reported (slide 4). The NRC assumptions that led to this policy are shown on slide 7. The subcommittee recommended "There is **no evidence at this time** for this subcommittee to recommend a reclassification of extravasation at the injection site for radiopharmaceuticals to be considered a medical event." (slide 16).







The ACMUI subcommittee did not reconcile its recommendations with new evidence that invalidates the 1980 assumptions–assumptions which led to the current NRC policy that exempts extravasations from misadministration/medical event reporting. In particular, there is no indication the subcommittee considered the submitted evidence that extravasations are no longer virtually impossible to avoid. Here is the evidence that was provided to the subcommittee:

1. Evidence from other healthcare settings demonstrates that extravasations need not be a frequent occurrence and are NOT virtually impossible to avoid.

   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.[1] Chemotherapy extravasation rates in the 1980s and 1990s ranged from 3-6%.[2, 3] 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.[4] 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%.[5, 6]

2. Low extravasation rates can also be accomplished in nuclear medicine injections. Technology can now prospectively identify nuclear medicine extravasations, help centers determine their associative factors, and measure improvement.
   - A multi-center quality improvement project paper [7] was recently published in the Society of Nuclear Medicine and Molecular Imaging's (SNMMI) Journal of Nuclear Medicine Technology (JNMT). The paper (available here) demonstrated that centers interested in improving their extravasation rates achieved statistically significant improvement ($p<0.0001$), and that improvement was sustained. The paper also concluded that variation in extravasations was significantly associated with technologists and centers ($p=0.0020$ and $p<0.001$).

     These peer-reviewed findings were not only published in the JNMT, they were also presented in two separate sessions at the June 2018 annual SNMMI meeting. The first session focused on using new technology to measure extravasation rate, and the second on how the technology enabled improvement. At the end of the annual meeting, a distinguished subject matter expert, Heather Jacene, MD. Associate professor in the Department of Radiology at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, highlighted twelve significant presentations from over 200 that were presented during the meeting.[8] Dr. Jacene included both of the extravasation presentations in her highlight session.

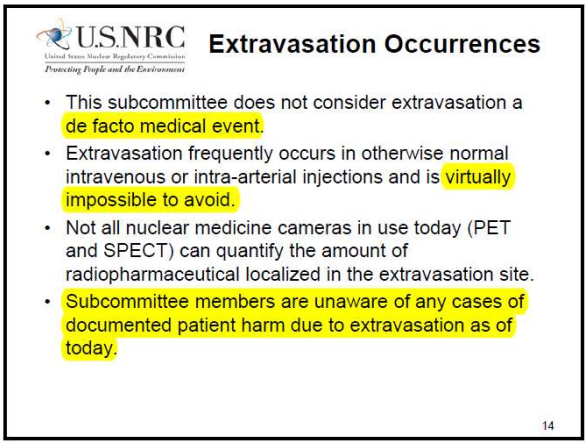
   - At the June 2019 annual SNMMI meeting, Chairman Palestro, Vice Chair Metters, and Subcommittee Chair Martin held an ACMUI session. During this session, they heard testimony from a nuclear medicine physician that, using new technology, his nuclear medicine center measured their extravasation rate, determined the potential causes of these extravasations, and then dramatically improved their rate over a three-month period (from 13% to less than 2% extravasation rate).

     A summary of this experience was also provided in a letter addressed to the subcommittee and is included in Attachment 1.

   - In addition to the evidence made available to the ACMUI subcommittee, there is evidence that, without the assistance of new technology, some nuclear medicine centers have successfully reduced their extravasation rates. For example, Christiana Care monitors nuclear medicine extravasations and maintains low rates by establishing an IV saline infusion prior to each injection. And as shared previously with the NRC by Dr. Abass Alavi, a nuclear medicine pioneer and leading expert, the University of Pennsylvania had a long-standing reputation of focusing on extravasation rate reduction. See Attachment 1.

In summary, the evidence is clear in 2019 that the assumptions that led the NRC in 1980 to exempt extravasations from misadministration reporting are no longer valid. Because the policy was specifically based on these assumptions, the subcommittee should have recommended that the NRC negate this policy.

B. Documented Patient Harm



It is true that not all extravasations will be considered medical events, because not all extravasations will exceed NRC reporting requirements. However, in the context of a patient safety culture, nuclear medicine centers may want to monitor these non-medical event extravasations in order to understand medical event “near misses.” Near misses are indicative that severe extravasations are more likely.

The subcommittee’s repeated point that *extravasations are frequent and are virtually impossible to avoid* disregards the evidence that clearly shows that extravasations can be significantly improved and nearly eliminated.

The subcommittee also presented that they are “**unaware of any cases of documented patient harm due to extravasation**” as of the date of their presentation, September 10, 2019.

A search of the FDA adverse event and European vigilance reporting databases leads one to a different conclusion. Our search identified 38 diagnostic and 17 therapeutic extravasations, resulting in 16 non-serious and 21 serious level adverse events associated with extravasations of radiopharmaceuticals, that reported outcomes of 1 death, 4 hospitalizations, 2 required interventions, and 16 other outcomes (see Attachment 2). The vast majority of these events were reported by the manufacturers, who are required to report to the FDA or EU regulatory body when they become aware of a qualifying event. Since the NRC currently exempts extravasations from reporting, manufacturers typically would be unaware when patient harm had been associated with an extravasation of their product and therefore, these patient events would not have been captured.

The NRC has also recognized the potential harm that relatively minor unintentional activity exposure may cause patients. In 1991, the NRC received a comment regarding a proposed rule change, that suggested low doses “would not produce any discernible harmful effects to the individual to warrant immediate reporting”. The NRC responded “Doses of the order of 25 rems (5 times the 5-rem annual dose limit) can produce discernible biological effects in the body in

the form of chromosome aberrations and changes in the white blood cell populations. Although the majority of these effects are temporary, they could be discerned." The NRC continued "However, irrespective of the potential for discernible effects, doses at these levels represent a major breakdown in the licensee's control over the radioactive material, and the Commission believes that it is important that NRC be promptly notified so that it can take actions, if necessary, to limit further consequences."

Significant extravasations of *diagnostic* radiopharmaceuticals can expose tissue near the injection site to much higher levels of unintentional radiation than the 25 rems noted by the NRC in the Federal Register comments above. While the damage to the tissue might not be immediately evident as described by the NRC in the cited example above, patients are receiving unintentional radiation exposure to their tissue that can far exceed the current NRC reporting limit of 50 rems (0.5 Sv). For examples, see Attachment 3, Cases 1 thorough 6. Two of these cases were provided to the NRC, ACMUI Chairman, and subcommittee earlier this year for their consideration.

A review of the literature finds that *radiotherapeutic* extravasations are more alarming due to higher activity levels and the use of alpha- and beta-emitters. In 2017, in the *European Journal of Nuclear Medicine and Molecular Imaging,* van der Pol et al conducted a systematic review of both diagnostic and therapeutic extravasations. Excerpts from this article provide insight on the topic of extravasation that should have been considered by the subcommittee and should be considered by the NRC, and include:

> *"Because of the character of the radiation, extravasation of therapeutic radiopharmaceuticals has the highest tendency to result in tissue damage, although some cases of tissue damage following the extravasation of diagnostic radiopharmaceuticals have been reported."*
>
> *"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 [sic] to under-reporting of skin lesions."*
>
> *"Clearance evaluation and dosimetry are often advised to be part of extravasation management. Different methods have been used, yielding a large range of tissue doses, due to uncertainties such as retained activity and the volume of the infiltrated tissue, as well as the use of worse case scenarios. Sequential activity measurements with probes or gamma-camera can give useful insight in biological half-life, as well as effectiveness of applied interventions."* [9]

Additionally, Bonta et al and Williams et al describe two separate radiotherapeutic extravasations that harmed patients, [10, 11] while two other papers cite cases of radiotherapeutic extravasations that exposed patients to doses that far exceed NRC reporting limits.[12, 13] Breen et al, describe a case in the *Journal of Nuclear Medicine* from **1991** that demonstrates the large doses to the skin or tissue that can result from a radiotherapeutic extravasation:

> *"Prior to injection, blood was withdrawn into the hub of the syringe to ensure correct i.v. placement. At the conclusion of 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."

"On the basis of serial counts, the half-time was 5.5 days at the IV injection site."

"…dose to the skin was calculated as 490 Gy and 245 Gy." [14]

This dose to the skin was between **490-980 times the NRC reporting limit of 0.5 Sv**.

Despite the extravasation reporting exclusion, the NRC has demonstrated foresight regarding the impact of misadministrations to diagnostic imaging and thus potential patient harm: "the significance of a diagnostic misadministration goes beyond the unnecessary radiation exposure if it results in a misdiagnosis." (FR Vol. 45, No. 95 31702)

Extravasations affect the quality and quantification of the nuclear medicine imaging, and compromised images can negatively affect patient care. This statement is supported by >50 peer-reviewed articles not discussed by the subcommittee or ACMUI. Some of these articles describe how patients receive additional imaging, unnecessary invasive procedures, and the wrong treatment. Below are quotes from some of these articles that suggest extravasations can result in the improper patient care.

"In the current nuclear medicine practice, injections sites that are out of the FOV, invisible infiltrations, and visible infiltrations underestimated due to the static nature of images, can all contribute to the interpreting and treating physicians reaching the wrong conclusion about staging and tumor response to treatment."

Kiser et al., Frontiers in Medicine 2018;5:143

"Quality control standards need to be assessed to avoid misinterpretations resulting from poor image quality due to a low count study (from poor labeling, dose infiltration), …."

Minoshima, J. Nucl. Med. 2016; 57:1316-1322

"Extravasation should not only be avoided but also reported in order to avoid false interpretations of the PET/CT exam."

Osman, Front Oncol. 2011;1:41

"When significant extravasation occurs, it can have a large impact on SUV values. This could be of critical importance for both diagnostic PET and evaluation of response to therapy."

Hall, J. Nucl. Med. Technol. 2006;47:115P

A summary of how patients can be adversely affected from the use of diagnostic images (PET and non-PET) that have been compromised by extravasations is included below, with the appropriate peer-reviewed articles as references.

PET

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.[15-23] 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 [24, 25] 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, [26] 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.[9, 27-30] See example below.

  - Masked metastatic disease caused by significant extravasation artifacts in image.[31]
  - Misinterpreting metastatic disease, identified near an expected injection site location, as an extravasation.[32]

- 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.[9, 31-49]
  - False positive bone scans.[50, 51]
  - 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.[28, 31, 41, 52-54]

- 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.[55] Because an extravasation removes radiotracer from circulation, 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.[55]
  - 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.[55] 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.

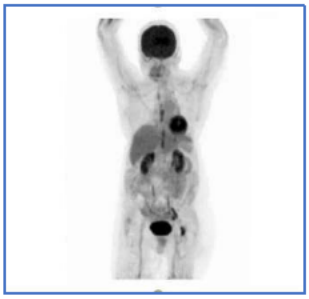
	Day 1 MTV Extravasated Injection	Day 5 MTV Ideal Injection	Understated
Lesion 1	7.43	11.34	34%
Lesion 2	5.57	10.66	48%
Lesion 3	27.77	41.07	32%
Lesion 4	0.88	2.93	70%

- Therapy assessment errors, due to understated quantification of baseline or follow-up scan.[30, 53, 56-66] 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%

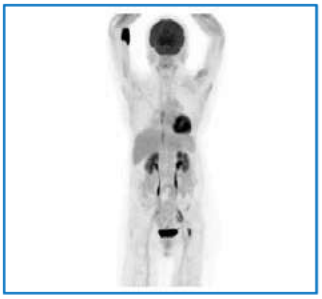
- An extravasated follow-up study, compared with a properly injected baseline study, may falsely indicate response to treatment. Treatment may not be working, but the images suggest tumor response. See hypothetical treatment assessment example using an actual extravasated patient below:

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.[22, 67] 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.[29, 68-70] Please note that a subcommittee member is a co-author on reference 63.

- An FDG neurological function study. An extravasation limits the FDG uptake in the brain and would adversely affect the reported results.[71]

- 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.[72]

- 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.[73] However, an extravasation may compromise imaging sensitivity and diagnostic capability.

Non-PET

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,[40] invalidate GFR studies, and may not be visible in the imaging FOV.[74, 75]
  - 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.[68]
  - 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.[76] 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.[77] In a study of 224 patients, 30 injection issues were documented.[78]

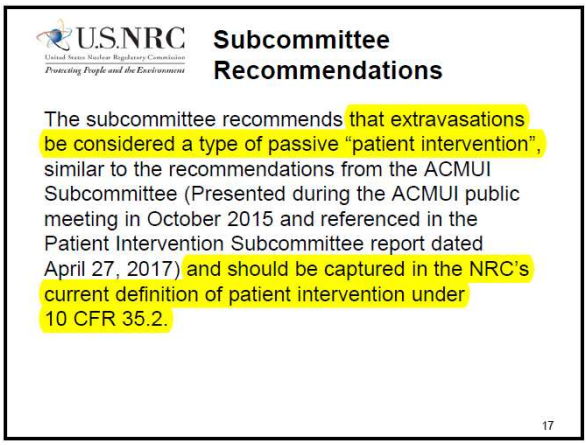
- Pulmonary embolism diagnosis. Ventilation Perfusion (V/Q) studies are used to diagnose the presence of pulmonary embolisms (PE), a particularly dangerous condition.

  - 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 [79] 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.[80] If an extravasation is suspected, the study is repeated the next day with additional patient radiation exposure.[81]

- 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 interpretation by physicians as significant breast abnormality [82]

While medical event reporting does not include patient harm as a mandatory criterion (10 CFR Subpart M § 35.3045), it is important to note that extravasations can not only meet the medical event criteria, but they also can and do lead to patient harm. The subcommittee’s statement that they **“are unaware of any cases of documented patient harm due to extravasation**” may lead the NRC to reach the conclusion that extravasations do not harm patients. That conclusion is incorrect. The adverse event and vigilance reporting databases contain reports that clearly document patient harm caused by radiopharmaceutical extravasations. And while it is impossible to directly assign long-term patient harm to diagnostic radiopharmaceutical extravasations, since they have never been monitored and tracked, it is not apparent the subcommittee considered this form of patient harm. Additionally, the subcommittee did not comment on the documented patient harm caused by radiotherapeutic extravasations. Finally, the subcommittee did not comment on the peer-reviewed evidence demonstrating how extravasations can adversely affect image quality and quantification and ensuing patient care.

C. Authorized User Responsibility, Not Patient Responsibility

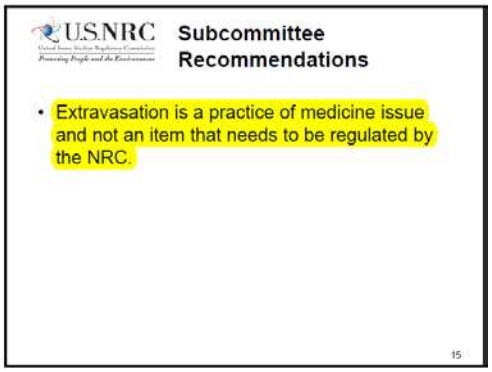


Patient intervention is defined by the NRC in 10 CFR 35.2 as "**actions** by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration." The subcommittee has suggested classifying extravasations as a type of patient intervention. This recommendation suggests that **patients** are responsible for the improper administration of a radiopharmaceutical and is not only inaccurate, but inappropriate. In "Report and notification of a medical event" (10 CFR 35 Subpart M § 35.3045), patient intervention justifies not reporting as a medical event. By suggesting that the NRC "capture" extravasations in the NRC's current definition of patient intervention the subcommittee is recommending that the NRC specifically exclude extravasations in the rule. This recommendation suggests a rule change that is inconsistent with the NRC's intent to ensure the proper administration of radiopharmaceuticals.

The subcommittee suggestion that extravasations should be classified as patient intervention is contradicted by the detailed comments made by the ACMUI members in 2008 and 2009 that specifically addressed the causes of extravasations. These causes included: inexperienced technologists, lack of training, venous access tool selection, technique, and a focus on quality and level of care taken in establishing an IV line. There was no mention that patients were a cause of extravasations. In the recently published multi-center quality improvement project, four factors were statistically associated with an increased likelihood of an extravasation. Only one, low patient weight, was not related to procedural factors. And in the review of the data from nearly 5,000 patients, only center- and technologist-level variation was statistically significant, indicating that proper administrations depended on which center and which technologist were administering the radiopharmaceutical.[7]

Lucerno's technology provides insight into potential associative factors for extravasations. Our findings lead us to believe that extravasation rates are technologist and technique dependent. For example, a new imaging provider recently became responsible for a hospital's remote location. Before the change of provider, the existing team had an extravasation rate in the low single digits. When the new provider and their new group of technologists took over the same location and same patient population, their extravasation rate over the first six months was >25%, indicating that the quality of the administration is a function of the technologist and their technique, not the patients.

D. NRC Jurisdiction



The subcommittee recommends that the improper administration of radiopharmaceuticals that unintentionally expose patients to doses that exceed NRC reporting limits should **not be regulated by the NRC**. Interestingly, this position is inconsistent with the patient safety position of the nuclear medicine community and the SNMMI regarding the NRC effort to modify Training and Experience requirements for Authorized Users. However, the subcommittee recommendation is entirely consistent with the nuclear medicine community's position on reporting misadministrations or medical events since 1980. In the Supplementary Information supporting 10 CFR part 35 final rule 39 years ago, the NRC cited that "ninety percent of the comments were opposed to the rule, most citing it as an unprecedented intrusion into medical practice." The NRC stated that the commenters were opposed because the reports would be open to public scrutiny, may cause undue patient alarm, and unwarranted malpractice suits. The nuclear medicine community has historically opposed not just extravasation reporting; they have opposed any reporting whatsoever, regardless of the amount of exposure to the patient.

Since the 1980 misadministration rule, NRC policy has been to protect patients from improper administrations of radiopharmaceuticals. In the Supplementary Information the NRC stated that they were requiring misadministration reporting to identify the underlying causes in order to correct them and prevent their recurrence. They also stated that their efforts were similar to the FDA's labeling policy efforts to increase patient understanding of the nature and the effects of prescription drugs as well as the right to know about a drug's risks and benefits; the NRC believes that "patients have a right to know when they have been involved in a serious misadministration." The GAO stated the NRC's misadministration reporting requirement was "clearly consistent with the NRC regulatory responsibilities and a necessary part of an effective nuclear medicine regulatory program."

In 1991, during an amendment to the 1980 rule, the NRC reaffirmed their 1980 position on the need to regulate the administration of radiopharmaceuticals (FR Vol. 56, No. 143 (July 25, 1991)).

In 1995, the NRC considered a case where a patient errantly received a diagnostic radiopharmaceutical. This misadministration exposed the patient to equivalent dose below the reportable threshold for part 35 but above the reportable threshold for part 20. In response, the NRC amended its regulations to clarify that the medical administration of radiation or radioactive materials to any individual is regulated by the NRC's provisions governing the medical use of byproduct material. The NRC went on to state "The medical administration of radioactive materials is a special use of radioactive materials that is best dealt with by specific regulations covering those administrations." In particular, the Commission believed that an administration to

any individual is and should be subject to the regulations in part 35. In this amendment the NRC confirmed that it would retain notification requirements for serious errors and would not interject itself into medical judgments for less serious errors. The NRC made the following supporting comments in the *Supplementary Information Part IV – Consistency with the 1979 Medical Policy Statement and Coordination with the ACMUI*:

> *On February 9, 1979 (44 FR 8242), the NRC published a Statement of General Policy on the Regulation of the Medical Uses of Radioisotopes. The first statement of the policy states, "The NRC will continue to regulate the medical uses of radioisotopes as necessary to provide for the radiation safety of workers and the general public." The proposed rule is consistent with this statement because it continues to provide for administrations of radioactive materials to be regulated under 10 CFR part 35. The proposed rule further clarifies that additional regulations are not considered necessary.*
>
> *The second statement of the policy states, "The NRC will regulate the radiation safety of patients where justified by the risk to patients and where voluntary standards, or compliance with these standards, are inadequate." The proposed rule is consistent with the statement because it clarifies that existing requirements concerning misadministrations continue to be concentrated on administrations having the greatest risk significance.*
>
> *The third statement of the policy states, "The NRC will minimize intrusion into medical judgements affecting patients and into other areas traditionally considered to be a part of the practice of medicine." The proposed rule is consistent with this statement because it limits its specific regulatory requirements for notification to the most serious errors in administration and minimizes requirements on errors in administrations that have less risk significance.*
>
> *Thus, the proposed rule is considered to be consistent with the 1979 medical policy statement.*

Of vital importance to the issue at hand today, on May 19, 1994, the ACMUI agreed that medical administrations should be regulated by part 35 rather than part 20. The ACMUI stated that notifying an individual of an error in administration below the misadministration threshold is the current practice and should not be regulated.

In 2002, NRC defined a reporting and notification threshold for serious errors.

Today, the NRC requires other issues in the administration of medical radiation to be reported. A review of the NRC website for reportable events revealed that accidental errors in the administration of diagnostic radiopharmaceuticals are reported. For example, on April 4, 2018, a licensee inadvertently delivered ~15 mCi of 18F-FDG onto a patient's shirt, exposing 100 cm^2 of skin on the patient's torso to ~2.8 Sv.

Furthermore, according to the NRC's Office of Public Affairs, NRC regulations aim to assure radioactive materials are used properly during medical diagnostics and treatments. The Office of Public Affairs also notes that a medical event does not necessarily mean that a patient has been

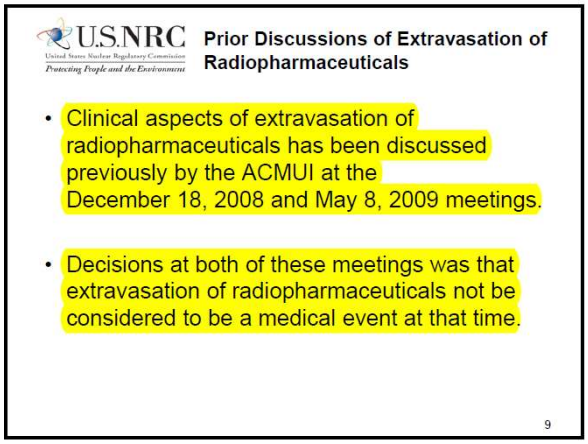
harmed, but it can mean that there may have been a problem in a medical facility's use of radioactive materials.

The subcommittee's recommendation "Extravasation is a practice of medicine issue and not an item that needs to be regulated by the NRC" is in clear conflict with NRC and ACMUI precedent. The recommendation is also inconsistent with recommended international practices, as outlined in the International Atomic Energy Agency's *Basic Safety Standards Requirement 41: Unintended and accidental medical exposure*. Requirement 41 states that "licensees shall ensure that all practicable measures are taken to minimize the likelihood of unintended or accidental medical exposures…as a result of human error." The requirement specifically addresses unintended or accidental exposures to the wrong tissue from medical treatments and diagnostic procedures and instructs licensees to calculate or estimate the dose, indicate corrective actions taken to prevent recurrence, report the event to the regulatory body, and notify the treating practitioner and the patient.

Problems in the delivery of radiopharmaceuticals that result in tissue dose exceeding NRC reporting limits are within the NRC jurisdiction and should continue to be reportable events. Extravasations are by definition problems in the delivery of radiopharmaceuticals and therefore should be reportable events.

E. Previous ACMUI Recommendations to Retain Exemption Not Based on Clinical Aspects

The subcommittee suggested to the ACMUI that previous ACMUI meetings had considered the clinical aspects of extravasations and decided to retain the 1980 exemption. Review of the transcripts suggests that primary concerns were operational in nature—difficulty in detecting extravasations, estimating dose, completing paperwork, etc. No evidence was referenced regarding the clinical effects of extravasations on patients.



In January 2008, the Boston VA reported a medical event due to extravasation of 18F-FDG. The NRC, based on the 1980 policy, asked the VA to retract the report. In December of 2008, the NRC approached the ACMUI for their opinion on whether the policy should be changed. The NRC suggested that the policy was nearly 30 years old. Since the policy's inception, new radiopharmaceuticals had become available that were more likely to exceed the NRC reporting limits. In addition, the NRC was concerned about patient safety as new radiotherapeutics were in development and being introduced. These administrations, as compared to diagnostic

radiopharmaceuticals, involve significantly higher activities and more damaging alpha and beta radiation.

Review of the ACMUI 12/18/2008 conference call transcript reveals that discussions of clinical effects of extravasations were anecdotal. There was no presentation of evidence regarding the clinical effects of an extravasation. Most of the discussion focused on the frequency and the known causes of extravasations, the effort associated with filling out the required medical event reports, and touched on therapeutic extravasations that would be further discussed during the 5/8/2009 ACMUI meeting. Below are some excerpts from the 12/18/2008 transcripts.

- Dr. Nag reiterated the 1980 assumption that "if it is routine that some radiopharmaceutical infiltrates in the normal course of a medical administration then infiltrations should not be viewed as a medical event." As previously described, extravasations need not be a routine outcome of a radiopharmaceutical administration, and therefore should be viewed as a medical event if they exceed the reporting requirement.
- Dr. Eggli expressed concern over the volume of reports that would be required. He stated that "infiltrations just always occur. If they were to become medical events, the NRC would be flooded with more medical events than it could manage."
- Dr Eggli shared his anecdotal observations on the frequency and clinical impact of extravasations. He stated that "in 30 years of clinical practice he had seen lots and lots and lots of infiltrations. I have **never seen an adverse clinical outcome**." He went on to say: "I think that complete infiltrations are not as common, although I see them with some regularity, particularly if you have a very young technologist staff. However, partial infiltrations, as a needle flips in and out of a vein, are really quite common and have neither impact on the diagnostic quality of the study, nor long-term adverse impact on the patient." Dr. Eggli did not comment on the impact of the <u>complete</u> extravasations.
- Dr. Eggli pointed out that with special care, extravasations can be avoided. He shared "we really take a whole different level of care in establishing our IV lines on therapeutic data [*sic*] emitters than you do typically on routine diagnostic studies. And I would think that you will find that the incidence of infiltration of therapeutic beta-emitters or other -- or alpha-emitters, when they become used, is going to be -- that I think is going to be fairly uncommon because of the quality of the IV that we establish to do that. When you inject a diagnostic radiopharmaceutical, they are often simply done with a straight stick of a needle. And you can perforate the far side of a vein or partially perforate the far side of the vein. If you get a good IV running and you run in 4- or 500 ccs of fluid prior to the administration of your therapeutic dose, I think the chances that you have a malfunctioning IV are likely to be detected before you administer a therapy dose. And we typically put in a fairly large volume of non-radioactive fluid through an IV where we plan to give a therapy, just to make sure that it really is where we -- a good IV, and that we are not putting anything into the tissues. You can put 10 or 20 ccs of fluid into the tissue and not notice it. It is much harder to put 4- or 500 ccs into the tissue and not notice it."
- Ms. Cindy Flannery from the NRC pointed out that the 18F-FDG extravasation reported by the Boston VA was an IV infusion prior to the injection. This indicates that there is still a chance that an IV infusion of a therapeutic might still infiltrate. She postulated that if that were to happen then the extravasation should be considered a medical event, since it would exceed reportable limits.
- Dr. Eggli responded to Ms. Flannery that the quality of technique used differs between diagnostic and therapeutic infusions. He explains "Even though it was given through an IV line, and we give all of our PET doses through an line, there are IV lines and there are IV

lines, and there are levels of care taken in establishment of the IV line that I, again, think are really quite different in therapeutic and diagnostic. The quality of the needle catheter used, a butterfly versus an angiocath or some other form of internal catheter makes a great deal of difference in the quality of the line and the likelihood of an infiltration."

- Dr. Eggli continued by agreeing that a therapeutic extravasation could be a reportable event. He shared "if we infuse and infiltrate a beta-emitter in large quantities, it is conceivable we could see tissue damage. I am not as -- I am not opposed to making a therapeutic infiltration of [*sic*] medical event, but I think it probably requires some more discussion about things I am probably not thinking about. But, again, I think it will be uncommon. And, again, let me say that not all IV lines are the same."

In the 5/8/2009 ACMUI meeting, the members discussed the difficulties associated with radiotherapeutic extravasation being considered a medical event. They discussed the difficulties in determining if therapeutic patients had been extravasated. An extravasation could be undetected since therapeutic patients are typically not imaged, technologists get little feedback, and any visual damage to the tissue happens at a later time. They also questioned the process one would use to identify the volume of tissue affected and the need to standardize dosimetry.

Ms. Flannery mentioned a radiotherapeutic that was reported to have caused a dose to the skin of 3.6 -7.1SV, but there was no discussion that this exceeded the NRC reporting limit of 0.5 Sv. Below are some excerpts of the 5/8/2009 transcripts.

- Dr. Nag, regarding whether the ACMUI should consider therapeutic extravasation that exceed reporting limits as medical events, stated: "we need to restate our previous position in the December 18th, 2008 meeting that accepted that it would not be considered a medical event. We always take the best precaution we can."
- Dr. Nag went to discuss his thoughts on radiotherapeutic extravasations and medical event reporting. "However, the first thing before us is, should NRC consider it as a medical event. Now if we consider this as a medical event, if we go through all the procedures and identify whatever- 3 or 4 or 5 - the patient will have to be informed; the physician have to be informed, blah blah blah [*sic*], and then - you have to go into all the reporting mechanisms. And therefore, I am thoroughly against this being reported as a medical event." We believe that the "-" that follows Dr. Nags reference of "3 or 4 or 5" refers to possible sieverts of exposure.
- When there was a motion to not consider therapeutic extravasations as medical events, Dr. Fisher questioned whether patients would be affected if an extravasation resulted in an inadequate supply of the therapy reaching the intended target. Dr. Eggli responded that this would "by the definition of medical event, yes, it's a medical event. However, this particular medical event is specifically exempted from being defined as a medical event. If that sounds circular, but this occurrence would meet the medical event criteria, but it is specifically exempted from consideration as a medical event." The Chairman then confirmed that the reason the case would not be considered a medical event was because of the 1980 policy in question.
- Mr. Lieto suggested that it shouldn't be considered a medical event because at least the entire dose was technically delivered into the patient's arm. Dr. Eggli pointed out that in the case where a large portion of the therapeutic was infiltrated that were it not for the extravasation exemption policy the extravasation should be considered a medical event because the dose was not delivered through the proper route of administration.

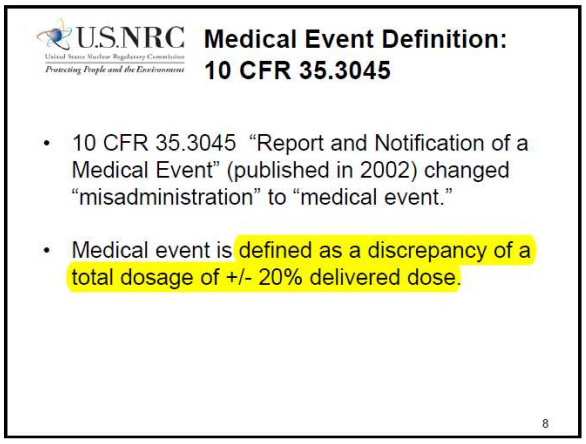
After considering the significant exposure that an extravasated therapeutic dose could provide to patient tissue and how an extravasation could negatively affect the delivery of the patient's

treatment, the committee still voted to retain the exemption policy. Two members abstained from the vote.

These transcripts revealed that anecdotal experience regarding clinical aspects was discussed. However, it is disingenuous for some ACMUI members to represent to the NRC that they **have never seen** patients harmed by extravasations. It is not uncommon for patients to only interact with technologists during their nuclear medicine procedures. Nuclear medicine physicians, radiologists, radiopharmacists, and radiation safety officers would not routinely be in a situation to physically examine all patients. [redacted], whose support letter is included in Attachment 1, has had 10 PET/CT procedures since her diagnosis of metastatic breast cancer and reports never interacting with any of the individuals listed above during her procedures. And as discussed during these meetings, it is likely that any visual damage to the tissue happens at a later time. Furthermore, in many cases, the ACMUI members would not know which patients had been extravasated. Additionally, since nuclear medicine extravasations have never been monitored and tracked, it is impossible to conclude that unintentionally exposing patient tissue to large doses of radiopharmaceuticals has not led to patient harm later in life.

From a review of the transcripts, it is clear that the vote to retain the exemption policy was not based on consideration of clinical effects to the patient. In these meetings ACMUI members clearly stated that diagnostic extravasations were frequent and caused by technologists, venous access methods, and injection technique. Additionally, members discussed examples where extravasations did or may exceed reporting requirements but were concerned that changing the exemption policy would result in increased medical event reporting. They hypothesized that therapeutic extravasations were significantly less frequent but could result in doses that exceed reporting limits and cause acute patient harm.

F. Extravasations Can Meet Medical Event Reporting Criteria



We have underlined the criteria for Medical Event reporting (10 CFR 35 Subpart M) that may apply to the topic of extravasation:

> *A licensee shall report any event as a medical event, except for an event that results from patient intervention, in which—*
>
> *(1) The administration of byproduct material or radiation from byproduct material, except permanent implant brachytherapy, results in—*

(i) A dose that differs from the prescribed dose or dose that would have resulted from the prescribed dosage by more than 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin; and

(A) The total dose delivered differs from the prescribed dose by 20 percent or more;

(B) The total dosage delivered differs from the prescribed dosage by 20 percent or more or falls outside the prescribed dosage range; or

(C) The fractionated dose delivered differs from the prescribed dose for a single fraction, by 50 percent or more.

(ii) A dose that exceeds 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin from any of the following—

(A) An administration of a wrong radioactive drug containing byproduct material or the wrong radionuclide for a brachytherapy procedure;

(B) An administration of a radioactive drug containing byproduct material by the wrong route of administration;

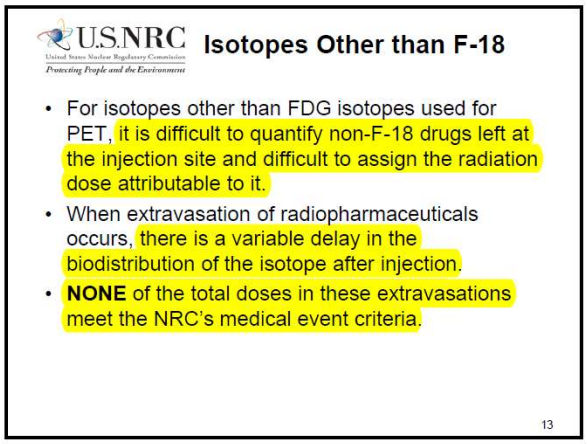
(C) An administration of a dose or dosage to the wrong individual or human research subject;

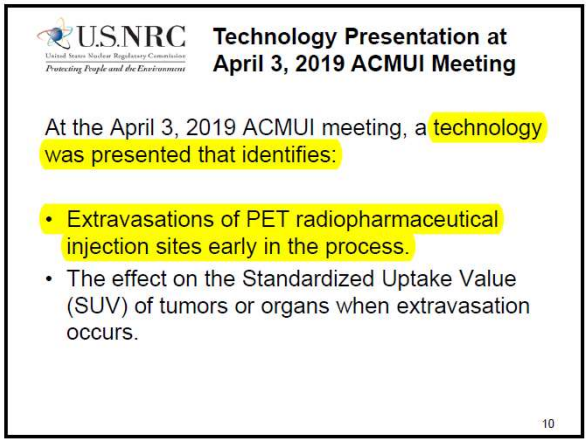
(D) An administration of a dose or dosage delivered by the wrong mode of treatment; or

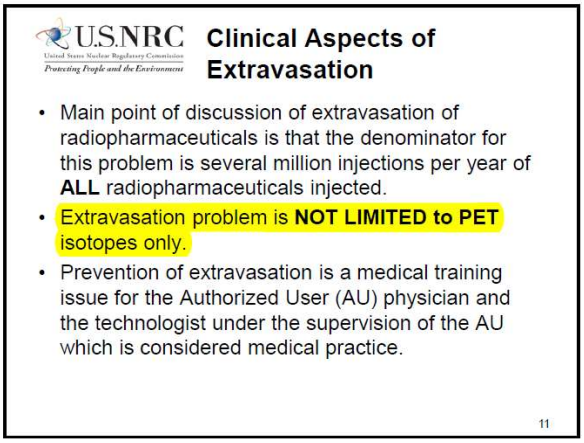
(E) A leaking sealed source.

To summarize, an extravasation meets medical event reporting criteria when the dose exceeds 0.5 Sv to tissue and either (i)(A) the total dose delivered differed from the prescribed dose by 20 percent or more, or (ii)(B) by the wrong route of administration.

G. Both PET and SPECT Extravasations Can Meet Medical Event Reporting Criteria







The technology that was presented in the April 2019 ACMUI meeting is not restricted to PET radiopharmaceuticals but can work with any radiopharmaceutical that contains a gamma emitter.

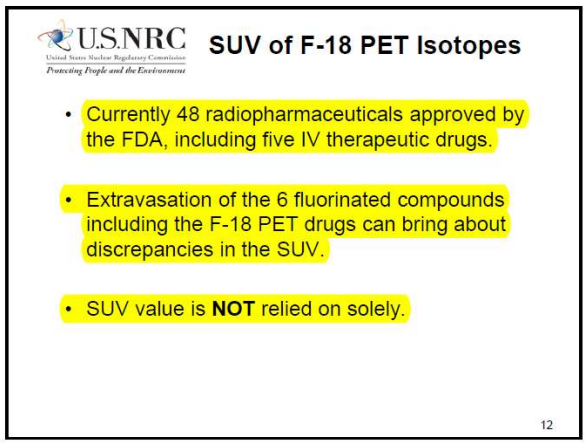
The subcommittee suggests that it is difficult to calculate extravasated activity and dose for non-PET radiopharmaceuticals. This should not be a reason to forego dosimetry of extravasated patients.

The subcommittee also suggests different radiopharmaceuticals will have different biodistributions after extravasated injections. Today, it is possible to characterize the delay in biodistribution. This leads to more accurate dosimetry than simple worst-case methods.

The subcommittee also stated that NONE of the total doses for extravasations of non-18F-FDG radiopharmaceuticals meet the NRC medical event criteria. The FDA adverse event and European vigilance reporting databases report 32 extravasations of non-18F-FDG radiopharmaceuticals. Some, or likely all, exceeded NRC medical event criteria. Furthermore, we have recently analyzed two 99m-Tc MDP extravasation cases. The estimated doses to tissue for these cases are 0.2-4.5 Sv and 1.5-7.5 Sv, all of which exceed the NRC reporting requirements. Please see Attachment 3, Cases 7 and 8.

Many physicians believe that because 99m-Tc is a lower energy gamma emitter, it will not result in high tissue dose. However, in the case of MDP, the polar, lipophobic, phosphate bonds cause the 99m-Tc to remain very close to the infiltrated site. Additionally, non-PET radiopharmaceuticals are often administered via a straight-stick technique, not followed by saline flush. As a result, the extravasated activity remains concentrated at the injection site. With a half-life of six hours, 99m-Tc extravasation can result in tissue dose that exceeds NRC reporting requirements.

H. Quantification Matters

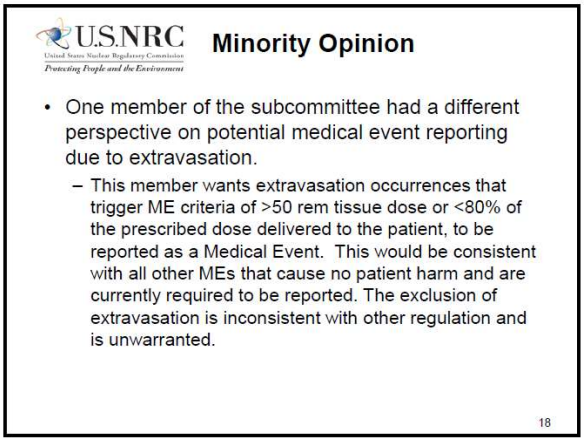


Regarding the role of quantification (SUV value) in the care of patients, it does not appear that the subcommittee considered the information provided by Dr. Dan Sullivan, the former Director of the National Cancer Institute's Cancer Imaging Program and the founder of the Radiological Society of North America's Quantitative Imaging Biomarker Alliance. Dr. Sullivan described the American College of Radiology's quality measure 4: *Use of Quantitative Criteria for Oncologic FDG PET Imaging*. This measure states that final reports of FDG PET scans should include at a minimum at least one lesional SUV measurement OR diagnosis of "no disease-specific abnormal uptake." Dr. Sullivan's letter is included in Attachment 1.

It also appears that the subcommittee did not consider the letter from Dr. Mark Yoffe, a University of North Carolina medical oncologist, who shared with the subcommittee how important the SUV measurement is to patient care and how it is commonly used today in oncology practices. Dr. Yoffe's letter is included in Attachment 1.

Additionally, it appears that the subcommittee did not consider the negative effect of an extravasation on metabolic tumor volume and the critical role that these volumes play in radiation oncology treatment plans.

I. Dissenting Opinion



One member of the subcommittee had a different opinion from their peers. Their recommendation is consistent with evidence. Now that we know that extravasations are not virtually impossible to avoid, they should no longer be accepted as a common occurrence. Extravasations should be reported when they exceed Subpart M criteria. As this subcommittee member pointed out, the exclusion of extravasation reporting is inconsistent with the regulation and is unwarranted.

The exemption of extravasations creates the following ironic situation: spilling radiopharmaceutical *on* a patient that results in a high dose to the skin is currently reportable, but spilling the same activity *into* a patient's tissue is not reportable. This inconsistency exists even though that extravasation results in higher tissue dose and compromises the diagnostic image used to guide their care. This is illogical and needs to be addressed.

Summary

In 2008 and in 2019, the NRC approached the ACMUI regarding the appropriateness of the 1980 policy that exempts extravasations from medical event reporting. In both instances the ACMUI recommended that the NRC retain this policy. Our reviews of meeting transcripts, meeting presentations, and peer-reviewed publications suggest that the ACMUI has not adequately considered the evidence in reaching their recommendations. Evidence exists today that nuclear medicine extravasations can be nearly eliminated in a short time period. Evidence also exists that diagnostic and therapeutic radiopharmaceutical extravasations can exceed NRC reporting and notification criteria and have harmed patients. Evidence from previous ACMUI meeting transcripts and from peer-reviewed publications demonstrated that extravasations are not the result of patient intervention, but rather are associated with administration technique. Based on the body of evidence, we conclude the ACMUI and the subcommittee have made an erroneous decision regarding this extravasation issue and therefore their recommendation should be rejected.

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Attachment 1: Support Letters

Perelman School of Medicine
University of Pennsylvania

Radiology

Abass Alavi, M.D., MD (Hon), PhD (Hon), DSc (Hon)
Professor of Radiology and Neurology
Director of Research Education

July 16, 2019

To whom it may concern:

I am a nuclear medicine physician with nearly 5 decades of molecular imaging experience. During my career, I have been an author on over 600 publications. I am the single most cited medical scientist at the University of Pennsylvania. I was the first physician to administer 18F Fluorodeoxyglucose (FDG) to a human being. In 1976, I was a key contributor to the publication of the first human positron emission tomography (PET) images of the human brain. I am sharing this contextual information to help explain my continuous support for efforts to address the issue of nuclear medicine injection infiltrations/extravasations.

Nuclear medicine imaging plays a vital role in the diagnosis and assessment of many important diseases. The administration of the radiopharmaceutical is a critical step in producing optimal quality nuclear medicine images. The vast majority of these images require that the radiopharmaceutical is injected into the venous system. An infiltration or extravasation results when part of the radiotracer dose is injected into the soft tissue surrounding the vein. As a result, the entire dose is not immediately circulating in the body.

An infiltrated dose decreases the sensitivity of the nuclear medicine image. It can also invalidate the quantification of these images, since knowledge of the actual dose administered into the systemic circulation is required to calculate the fraction of the dose in a volume of interest. Infiltrations cause patients to be unintentionally exposed to unnecessary radiation near the injection site that often exceed the Nuclear Regulatory Commission's (NRC's) reporting limits. The frequency of infiltrations in some nuclear medicine practices is surprisingly common, but can be improved. As the former Chief of Nuclear Medicine and the Medical Director of Positron Emission Tomography Center at the University of Pennsylvania, I ensured that our team focused on improving injection quality. For decades our center successfully focused on reducing infiltrations; however, the vast majority of centers do not even monitor their injections for infiltrations. They don't even know when they are relying on compromised images to help guide patient treatment.

The lack of awareness about this issue is related to a lack of reporting requirements regarding infiltrations. At this time, the NRC and their Advisory Committee on the Medical Use of Isotopes are considering reversing an internal NRC policy from 1980 that resulted in exempting all infiltrations from being reportable events, even though some infiltrations significantly cause local exposures that exceed the NRC reporting limits. This policy was based on opinions that infiltrations are virtually impossible to avoid. Today, there is mounting evidence that shows infiltration rates can be significantly improved. By reversing their internal policy, the NRC can

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play an important role in reducing infiltrations. This will improve patient care and safety. When providers are required to report infiltrations that exceed reporting limits, they will begin to monitor injection quality and implement quality improvement efforts to reduce infiltrations. This simple change can positively impact lives and reduce healthcare waste/costs. I ask you to encourage the NRC to reverse this internal policy and remove the infiltration reporting exemption.

Thank you for your consideration of my request.

Abass Alavi

Abass Alavi, MD.
MD (Hon), PhD (Hon), DSc (Hon)

Dr. Christopher Palestro
Chairman of the Advisory Committee on the Medical Use of Isotopes
Nuclear Regulatory Commission

Dear Dr Palestro,

I am writing to you as co-inventor of the combined PET/CT scanner (along with Dr Ronald Nutt) that brought PET scanning into mainstream radiology for imaging oncology patients. The device became commercial in 2001 and now there are around 5000 such scanners worldwide. Over two million PET/CT scans are currently performed in the USA annually. Increasingly, PET is being used to monitor and guide therapy in cancer patients, a procedure that requires measuring the uptake of the radiopharmaceutical by the tumor. Such quantitation requires that the injection of the radiopharmaceutical be performed efficiently (without infiltration) and reproducibly.

For the last several years I have been a non-compensated scientific consultant for Lucerno Dynamics, the company that manufactures a simple device capable of monitoring the radioactive injection in PET studies. Since the device can provide a time-activity curve of the presence of the radiopharmaceutical near the injection site before the patient is imaged, it is now possible to reliably estimate the local radiation dose to the tissue in the event of an infiltration. **Given this new information I would respectfully request that infiltrated injections that exceed the reporting limit are mandated to be reported, and that the current exemption from reporting such infiltrations be removed.** While infiltrations in PET and other nuclear medicine procedures may be rare, a significant infiltration may deliver a high local radiation dose and it should be reported. Such infiltrations critically affect the integrity of the imaging study and may have consequences for the management of the patient.

As a final point, in addition to the over two million PET scans performed each year in the USA, some 40 – 45 million nuclear medicine studies are performed, also requiring a radioactive injection to the patient. Thus, even a low rate of infiltration potentially represents a radiation protection issue for a significant number of patients. The Lucerno device could also provide such a monitoring service for these nuclear medicine studies such that infiltrations which exceed the reporting limit be identified ***and reported***.

If you have any questions or require further information, please do not hesitate to contact me.

Sincerely,

David W Townsend PhD, PD, DSc, FRCR
Professor of Radiology, Fellow, IEEE

DUKE UNIVERSITY MEDICAL CENTER
Department of Radiology

June 6, 2019

Dr. Christopher Palestro

Chairman of the Advisory Committee on the Medical Use of Isotopes

Nuclear Regulatory Commission

Dear Dr. Palestro,

I am a diagnostic radiologist at Duke University Medical Center, and I also have specialty certification in Nuclear Radiology (American Board of Radiology-Nuclear Radiology,1977, Cert. #20014). In my entire 40-year career in radiology I have been focused on means to improve the reproducibility of results that patients receive when they have clinical imaging studies done. From my earliest days in radiology (1978-present) I have repeatedly lectured and written that patients should get the same result if they go to the radiology department on a Wednesday than if they go on a Tuesday. Sadly, that is too often NOT the case. The reasons for this day-to-day variability are complex and reflect the use of different scanners, software, technologists, local operating procedures, and different radiologists. (As an example of my long-term interest and concern about this issue I list one of my early (1983) references at the bottom of this letter, pertaining to the variability in interpretation of lung ventilation-perfusion scans.)

One strategy to reduce variability, and a very important one, is to extract objective, reproducible, quantitative results from clinical imaging scans. Since all clinical imaging studies today are digital, this is very feasible. In 2007, with support from the Radiological Society of North America (RSNA), I left the National Cancer Institute (NIH) and formed the Quantitative Imaging Biomarkers Alliance (QIBA) [https://www.rsna.org/en/research/quantitative-imaging-biomarkers-alliance]. QIBA now has about 20 committees working on a variety of quantitative imaging biomarkers, and over 1000 participants representing more than 150 stakeholder entities and organizations. The FDA recently released a draft guidance for quantitative medical devices [https://www.fda.gov/media/123271/download] and they reference QIBA and some of our QIBA publications as the source for their definitions and concepts used in the guidance (Ref 2 below is in the Guidance).

One of our first QIBA committees dealt with the standardized uptake value (SUV) from FDG-PET scans [http://qibawiki.rsna.org/images/1/1f/QIBA_FDG-PET_Profile_v113.pdf]. Rigorous attention must be paid to all potential sources of variance in order to obtain reproducible, clinically meaningful SUV results. This is entirely possible in nuclear medicine departments that care about the quality of their results.

Because of my interest and expertise in the issues of imaging scan quality assurance and quantification, Ron Lattanze of Lucerno contacted me a couple of years ago to provide scientific consultation services to Lucerno, primarily involved in reviewing and editing their draft scientific publications. However, I have

no financial interest in the company or their products, and I am not being paid to write this letter. I attended the NRC meeting on April 3, 2019, and am writing this letter to add my perspective to the discussion that occurred at that meeting.

There is no question that reproducible, quantitative SUV results from FDG-PET scans are increasingly viewed as important in clinical oncology – both in routine clinical practice as well as in clinical trials. Here are some supporting points:

- In 2010 a colleague of mine, Tracy Jaffe, and I surveyed several hundred oncologists at NCI-funded cancer centers about tumor measurements (mostly about measurements on CT), and found that more than half of oncologists also expected SUV to be provided from FDG-PET scans (ref 3). My interactions with oncologists in many venues over the past decade indicates that the proportion who want to use SUV in patient management decisions is steadily increasing,
- In 2018 the ACR approved a quality performance measure entitled: Measure 4: Use of Quantitative Criteria for Oncologic FDG PET Imaging [https://www.acr.org/-/media/ACR/Files/Quality-Programs/Diagnostic-Imaging-2018-Measure-Set-Final.pdf?la=en], which says in part: "Final reports for FDG PET scans should include at a minimum: … d. At least one lesional SUV measurement OR diagnosis of "no disease-specific abnormal uptake". And it goes on to note: "Often injection-site infiltrates, such as arms, or attenuation-correction errors can significantly alter SUV values in lesions, leading to false conclusions." Thus, providing an accurate SUV result for ***every*** cancer patient is an expected performance measure by the American College of Radiology.
- The 2018 Guidelines of the EANM, referenced on the SNMMI web site [http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414&navItemNumber=10790#Onc], state: "Report any problems with FDG administration and image the injection area if extravasation is suspected." This acknowledges that extravasation is a problem to be avoided, but it leaves open the question as to how an extravasation would "be suspected".
- A recent example from the oncology literature concerning the increasing interest in using SUV data comes from the Eighth Edition of the Cancer Staging Manual (Ref 4), where the chapters on lung and breast cancer staging (written by oncologist expert panels) recommend that SUV values now be recorded into all cancer registries at all cancer centers:

  P. 441 (lung) "PET should provide the following information:

  a. Presence of normal or abnormal uptake in the primary tumor and quantification by maximum standardized uptake value (SUV-max).
  b. Presence of normal or abnormal uptake in hilar and mediastinal nodes and quantification by SUV-max."

  "Although SUV-max is subject to many intra- and interinstitutional variations, it is important to record it at initial staging to assess metabolic tumor response after treatment, especially after induction treatment to evaluate the possibility of tumor resection. SUV also has shown prognostic value, at least for Stage I-III squamous cell carcinoma and adenocarcinoma."

  p. p 601 (breast) - "18F-FDG-PET reports should include standardized uptake values (SUVs) of the identified lesions."

- Manufacturers are promoting the accuracy and precision of SUV from their devices, because increasingly their customers understand the value of this and expect such precision:

  [https://www.gehealthcare.com/products/molecular-imaging/discovery-mi]

  https://www.siemens-healthineers.com/en-us/molecular-imaging/xspect/syngo-via/technical-details

  https://www.usa.philips.com/healthcare/product/HC882456/ingenuity-tf-petct-system

  https://us.medical.canon/products/computed-tomography/celesteion/technology/

  All of the PET/CT scan manufacturers strongly emphasize in their marketing materials the quantitative ability of their devices, and they would not invest the engineering resources to accomplish this if they did not believe their customers wanted this level of quantitative accuracy. But obviously these devices cannot provide accurate and reproducible SUV calculation if there has been infiltration of the injection.

My comments above have been focused on the need for accurate and reproducible quantitative results in oncologic FDG-PET scans because that is my primary area of expertise. However, the literature clearly supports the need for similar reproducible quantification in several other clinical areas, such as cardiology. You have an expert from that domain and a thought leader regarding the importance of quantification on your committee - Vasken Dilsizian, M.D (Ref 5) – and he could certainly provide more context for the cardiology arena and other clinical applications. For example, a recent joint position paper from the SNMMI and ASNC on myocardial blood flow measurements (Ref 6) includes this point:

- "Consistent tracer injection profiles improve the reproducibility of MBF measurements."

Similar publications can be found recommending rigorous image acquisition parameters for PET scanning of cardiac inflammatory conditions (Ref 7), sarcoidosis (Ref 8) and many other conditions.

As discussed at the April 3, 2019 NRC meeting, infiltrated injections of FDG can also adversely affect qualitative, visual interpretations of oncologic PET studies, and I will not elaborate on that here because my professional focus has been on the need for reproducible quantitative results. Also, as stated at the April 3 meeting, and documented in the various materials provided to the committee by Lucerno, infiltrated injections are much more common in nuclear medicine than most people realize, and this is a fixable problem. The incidence of infiltrations in other aspects of healthcare delivery is much lower, and there is clear evidence that the rate of infiltrations can be significantly reduced by the standard QA methodology of documenting the occurrence and providing feedback to those responsible.

I strongly endorse the current process of having the NRC and ACMUI re-evaluate the 1980 NRC policy that states that infiltrations are virtually impossible to avoid and therefore should not be considered a misadministration or a reportable event, even if the infiltration exposed patients to radiation levels that exceed Subpart M reportable limits.

I strongly encourage the NRC and ACMUI to modify this 1980 policy and remove the infiltration reporting exemption. Such a change in policy would lead to a significant improvement in the reproducibility of SUV measurements, and greatly improve their clinical usefulness. This will translate into a major benefit to patients in this era of precision medicine.

Thank you for the opportunity to provide these thoughts and opinions,

Sincerely,

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References:

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June 3, 2019

Dr. Palestro
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Dear Dr. Palestro:

Good day. I am the Medical Director of molecular imaging at the Carilion Clinic in Roanoke, VA. I am aware the ACMUI and the NRC are re-evaluating policy language put forth in 1980 regarding exempting providers from reporting requirements in the event of radioisotope extravasation/infiltration. As you recall, that policy was based on an opinion that these events “happen frequently and are virtually impossible to avoid”. I am in agreement that this stance should be reconsidered.

For the past several years, our practice has been using a device that allows us to monitor our injections during PET-CT procedures when administering the intravenous isotope. The device consists of a PET detector crystal that is placed in proximity to the injection site and monitors the delivery of the isotope in real time and can alert the radiologist as to the possible occurrence of an infiltration. For all the years I have been in practice, when I found a patient to have a significant infiltration, I would have the patient return on another day for a repeat scan. Prior to using this new device, I had to rely on visual evaluation of this by placing the injection site, whenever possible, in the imaging field of view. Now with this device, we scan patients with the injection site out of the field of view.

This device has also been instrumental in one of our QA/QC projects where we monitored our technologists for infiltrations over a period of time and found a rate of infiltration of about 13%. When we did an analysis, with statistical review of the data, we had the technologists revise their injection and IV placement techniques. These changes were driven by infiltration associative factors identified by these data. With these modifications, the technologists were able to get their infiltration rate down to about 2%. At the current time,

our infiltration rates are less than 2% and we continue to monitor our technologists going forward.

It has been my stance in practice that when in a test-retest environment, it is critical that all the input parameters for a given test be reproduced at the time of retest to mirror those at the time of the initial test. One of these parameters is knowledge that the radioisotope is delivered systemically. When there is a large infiltration, this can impact the accuracy of the SUV measurement. We have had several cases that exemplify this. Just in the past week, we had a patient returning for follow-up for metastatic cancer. We had a severe infiltration which required that the patient return for repeat scan. The SUVs that were measured on the infiltrated scan suggested a partial response to therapy but the repeated scan without infiltration indicated stable and possibly progressive disease.

I hope that you and the review committee will consider revising the current position on infiltrations. If large infiltrations that exceed NRC reporting limits are required to be reported then providers will begin monitoring their injection quality and implement QA/QC projects like we did to improve our process. This will result in improved imaging, better patient care, less waste, and will also improve patient safety.

Respectfully submitted,

Jackson W. Kiser, MD

CARILION CLINIC

Dr. Christopher Palestro

Chairman of the Advisory Committee on the Medical Use of Isotopes

Dear Dr. Palestro,

I recently read an article, *Quality Improvement Initiatives to Assess and Improve Positron Emission Tomography/Computed Tomography Injection Infiltration Rates on Multiple Centers*. I am writing to express my concerns as this topic has significant implications for the care of the cancer patients.

As an oncologist I rely on the accuracy of the PET image at 3 critical points: 1) accurate staging of newly diagnosed cancer patient 2) response to therapy (radiation, chemotherapy or combined) and 3) continued surveillance for recurrence, post therapy. An infiltrated dose of radiopharmaceutical decreases the sensitivity of the nuclear medicine image. Significant infiltration at **any** time could negatively impact the total care and prognosis of the cancer patient. i.e. patients deemed stage I, could be more advanced stage; patients thought to be responding when they are not, because they have recurrent disease and would continue with ineffective therapy and finally "early" recurrent disease would be missed and the cycle of inaccuracies would continue.

I am aware that nuclear medicine infiltrations are currently not monitored primarily because the injection site is out of the field of view in a significant number of patients. For the reasons stated above, it is critical that every injection should be evaluated for significant infiltration and reported to the referring physician in order to increase the certainty that appropriate interpretation and measures are taken in the care of the cancer patient.

I urge the NRC and Advisory Committee on the Medical Use of Isotopes (ACMUI) to modify the 1980 policy that exempts the reporting of infiltration. This would address the concerns I have stated above. Doing so will ensure that all therapeutic decisions could be made with more confidence, knowing that the PET scan injections were done correctly and with utmost certainty. And, if a significant infiltration has occurred the oncologist and or nuclear medicine physician can be given the choice to repeat the scan.

Sincerely,

Mark Yoffe MD

Rex Hematology Oncology, UNC Health Care

4420 Blue Ridge Rd.

Raleigh, NC, 27607

THELEAPFROGGROUP

August 29, 2019

Dr. Christopher Palestro:
Chairman of the Advisory Committee on the Medical Use of Isotopes
U.S. Nuclear Regulatory Commission

Dear Dr. Palestro:

On behalf of The Leapfrog Group, a national nonprofit organization representing employers and other purchasers advancing the quality and safety of American health care, I am writing in support of the NRC and ACMUI's reevaluation of NRC's 1980 determination related to infiltrations and medical event reporting [45 FR 31703].

The Leapfrog Group was founded in 2000 by large employers and other purchasers of health care, and our flagship Leapfrog Hospital Survey collects and transparently reports hospital performance, empowering purchasers to find the safest, highest quality care and giving consumers the lifesaving information they need to make informed decisions. We also assign letter grades to hospitals based on their record of patient safety, helping consumers protect themselves and their families from errors, injuries, accidents, and infections. The Leapfrog Group reports data on over 2,000 hospitals nationwide.

Diagnostic errors, such as those caused by infiltrations, are a significant concern for purchasers as well as many other stakeholders nationally. Unfortunately, data on diagnostic errors is virtually nonexistent. That is why we are interested in new data demonstrating the prevalence and consequence of infiltrations in nuclear medicine procedures. We are aware that infiltrations can have a serious impact on the quantification of a PET/CT scan, potentially affecting the care that a physician provides a patient, and can result in unnecessary radiation exposure.

In addition, we urge NRC, through this reevaluation, to ensure that patients are informed of radiological injections that result in infiltrations and that there is full public reporting of this information.

In our judgment, monitoring of nuclear medicine injection quality and reporting of infiltrations to the Nuclear Regulatory Commission would improve the quality, safety, and value of health care, and would increase transparency in our health care system.

Thank you for your attention to this matter, and please do not hesitate to contact me if you have any questions.

Sincerely

Leah Binder
President and CEO
The Leapfrog Group

Dear Maryann Ayoade,

I am writing to express my concern about the Medical use of Isotopes. Please forward this to Dr. Palestro in addition to the other members of the ACMUI subcommittee.

On January 31, 2017 I was diagnosed with stage IV metastatic breast cancer, 7 years after being treated for stage 1 estrogen positive breast cancer. This stage IV cancer was NOT expected in that I had a very small tumor and had no lymph node involvement with my original diagnosis. Unfortunately, in December of 2016, I was diagnosed with what was thought to be a local recurrence of the original breast cancer. I, however, pushed to have a PET scan done to be certain it was just a local recurrence. After finally receiving the PET scan, two nodules in lymph nodes near my lungs were discovered, then biopsied and I received the hard and scary Stage IV metastatic breast cancer diagnosis based on that PET scan.

That PET scan enabled me to be diagnosed at a very early stage of metastatic disease and I immediately began treatment to prolong my life. I am over 2 years past the diagnosis and have remained stable enough to stay on my first line of treatment, which is very good news.

As you can imagine, as someone who has undergone numerous nuclear medicine procedures in order to diagnose, treat and monitor my Stage IV metastatic breast cancer, I feel strongly that nuclear medicine centers should use best practices to ensure proper injection administration and thus, the accuracy of the resulting imaging. I am aware that nuclear medicine infiltrations are currently not monitored by providers and that they can negatively affect patients, through unintended radiation exposure to the patient's tissue near the injection site and through using compromised diagnostic images that result in improper treatment, such as:

- Under-staging of disease (missing metastasis, unnecessary surgery for what is thought to be a single lesion)
- Over-staging disease (treating metastatic disease and withholding potentially lifesaving regional therapy, false positives).

I have PET scans every 12 weeks to monitor disease progression. My entire treatment plan is dependent on the accuracy of the scans. It is not an overstatement to say, that my LIFE is dependent on the accuracy of the scans. I know that the injection process is critical to the accuracy of my images. I am also aware that the injection process will depend on the effectiveness of my technologists at that moment. If any of my multiple injections had been compromised, it is concerning to me that radiologists and treating physicians may have unknowingly under-staged or over-staged my disease – or otherwise made a therapeutic planning error – as a result of an undetected injection issue. It is even more concerning that I would be unaware of this situation, too.

Nuclear medicine providers and federal regulators should be doing everything in their power to improve the quality of these injections so that images reflect reality and treating physicians can plan treatment accordingly. I am encouraged that the NRC and ACMUI are currently in the process of evaluating a 1980 NRC policy that exempts infiltrations that exceed Subpart M reportable limits from being submitted as medical events.

I strongly urge the NRC and ACMUI to modify this 1980 policy and remove the infiltration reporting exemption. Patients and our doctors need to know when their injections have been infiltrated. We should be given the choice to repeat the imaging procedure rather than have our doctors use a below

average image to help determine our care. There also should be transparency about nuclear medicine injection infiltrations by center, so patients can know where to go for the highest quality imaging.

I would welcome the opportunity to communicate directly with the ACMUI Patient Advocate if they are interested in hearing the perspective of a nuclear medicine patient on this matter.

Sincerely,

[redacted]

[redacted]

Raleigh, North Carolina

[redacted]

[redacted]

Dr. Christopher Palestro
Chairman of the Advisory Committee
Medical Use of Isotopes

July 19, 2019

Dear Dr. Palestro,

I want to share with you my experience and thoughts following the diagnosis and treatment for Stage 4 Lymphoma. I am not in the medical field and quite frankly, had basically no experience with cancer or cancer treatment in my 56 years. However, I have gained considerable knowledge and experience in this area over the past twelve months.

On the afternoon of July 17, 2018, I had a PET scan at Wake Forest Baptist in Winston Salem, NC. During the twenty-minute ride home from the scan, I got a call from Dr Vaidya, my oncologist, advising me that I would begin chemo at Baptist the following morning. Based on the scan, my cancer was so extensive (from my neck to my left thigh) and aggressive that treatment must be immediate. Also, the scan found a crack in my lower back (hip) believed to be a result of the cancer and it caused great concern. I checked into Baptist at 7:45am the following day and life was changed.

I was infused with chemo drugs (R-EPOCH) for five straight days (in the hospital) and then allowed to "recover" the next sixteen days. This twenty-one-day cycle would repeat six times over the next five months. On August 23rd (after round two), I had a second PET scan at Baptist to verify my progress. Remarkably (according to Dr. Vaidya), the visible signs of the cancer were no longer visible on the scan! This was terrific news! The treatments continued over a six-month period and January 12th, 2019, I had a third PET scan to evaluate the full results of the chemo treatments. The scan showed no "hot spots" and I was believed to be cancer free! Certainly, that is awesome!

My reason for writing and sharing this background is a concern I have over the results of the PET scan. During my first two scans, Baptist had a technology in place so they could evaluate the effectiveness of the radioactive dye injection as part of the PET scan. This was great comfort to me to be able to know the dye was injected properly and was circulated throughout my body. I knew then that the results of the PET scan could be trusted!

During my last PET scan in January, this technology was no longer being used and I was alarmed by this. What if the dye didn't fully make its way throughout my body? What if it wasn't done well? Who would know? Nobody! The results of the PET scan didn't show any "hot spots" but can I be sure there isn't some cancer remaining and growing due to a poor injection?

I have a six-month check-up coming in August 2019 and another PET scan. My hope is that this technology can and will be used for my PET scan so I can trust the results of the scan are complete and accurate. Without this technology, I don't know. I understand that the NRC does not currently require infiltrations to be reported, even if patients are being exposed to high levels of radiation that exceeds the NRC reporting limits. This policy should be changed.

I am not a doctor and am not even in the medical field. However, I do understand the need for encouraging and possibly even mandating the use of this technology for cancer patients. Why would we not want to monitor and document the success of the dye injection, which gives us the most accurate PET scan. For people like me, it is life and death.

Warm regards,
[redacted]

WISCONSIN COLLABORATIVE *for* HEALTHCARE QUALITY

June 12, 2019

Dr. Christopher Palestro
Chairman of the Advisory Committee on the Medical Use of Isotopes
Nuclear Regulatory Commission

Dear Dr. Palestro:

As President/CEO of the Wisconsin Collaborative for Healthcare Quality (WCHQ), I am writing with regards to the current work of the Nuclear Regulatory Commission (NRC) and Advisory Committee on the Medical Use of Isotopes (ACMUI) to evaluate the 1980 NRC policy regarding the exemption of infiltrations that exceed Subpart M reportable limits from being submitted as medical events.

By way of background, WCHQ is a nationally recognized regional health improvement collaborative devoted to performance measurement, public reporting, and quality improvement. We are a voluntary statewide consortium of healthcare organizations in Wisconsin that has led the nation in measuring and reporting the quality of care in physician groups. Our staff possess decades of experience and expertise in data architecture, performance measurement, quality improvement and practice transformation initiatives. The work of WCHQ is focused on dramatically improving the health and increasing the value of healthcare for the people of Wisconsin and given WCHQ's public reporting mission believe that performance measurement and public reporting promote greater transparency, improvement, and efficiency in healthcare.

Recently, WCHQ has become aware of the issue of nuclear medicine injection infiltrations. We have reviewed information regarding their surprising frequency and have learned that infiltrations can lead to patient harm through inaccurate diagnosis, which leads to unnecessary or inappropriate procedures. In addition to the impact on the patient, such procedures can also be viewed as contributors to healthcare waste.

We are also aware that providers do not routinely monitor nuclear medicine injections, but do monitor many other injection processes, such as chemotherapy and contrast CT injections. We know that in chemotherapy and contrast CT injections the infiltration rates are less than 1% and have been methodically studied and improved over time.

Given this, we would encourage the NRC and ACMUI to modify the 1980 policy and remove the infiltration reporting exemption. By ensuring that providers report infiltrations that exceed Subpart M limits, the NRC would increase transparency to the issue and encourage providers to improve their injection processes, which in turn will lead to improved patient care and safety.

Sincerely,

Christopher Queram
President/CEO
WCHQ

WCHQ | PO Box 628578, Middleton, WI 53562-8578 | 608-826-6838 | www.wchq.org

Attachment 2: Adverse Event Reports from Extravasations

Adverse Event and Vigilance Reports

Radiotracer	Diagnostic or Therapeutic?	# of Cases	Concomitant Product Names	Reason for Use	Sex and Age	Event Date	FDA Reported Date	EU Reported Date	Reaction(s)	Serious/Seriousness	Outcomes	Sender	Country where event occurred
DaTscan (I-123)	Diagnostic	1	N/A	diagnostic procedure, neuroblastoma	NS (1)	11/15/2015	12/8/2015	N/A	product administration error, no adverse event	serious	other outcomes	GE Healthcare	DE
fluorodeoxyglucose F-18	Diagnostic	1	N/A	PET/CT Scan	F (86)	UNK	N/A	6/22/2018	extravasation, peripheral swelling	NS	recovered/resolved	IBA Pharma	EEA
fluorodeoxyglucose F-18	Diagnostic	1	N/A	PET/CT Scan	F (51)	UNK	N/A	5/2/2018	extravasation, injection site pain	NS	recovered/resolved	EEA Regulator	EEA
fluorodeoxyglucose F-18	Diagnostic	1	Iomeprol	PET/CT Scan	F (34)	UNK	N/A	4/10/2018	extravasation, hypoaesthesia, injection site erythema	NS	recovered/resolved	EEA Regulator	EEA
fluorodeoxyglucose F-18	Diagnostic	1	N/A	UNK	NS	UNK	N/A	8/9/2017	application site extravasation	NS	unknown	EEA Regulator	EEA
fluorodeoxyglucose F-18	Diagnostic	1	N/A	Imaging	F (55)	UNK	N/A	4/19/2018	injection site extravasation, injection site pain	NS	recovered/resolved	EEA Regulator	EEA
Lutathera (Lu-177)	Therapeutic	1	Ondansetron, tranxene, emend, methylprednisolone	carcinoid tumor of the small bowel, drug toxicity prophylaxis, prophylaxis of nausea and vomiting	M (70)	9/21/2017	7/4/2018	N/A	infusion site extravasation	serious	other outcomes	Advanced Accelerator Applications	FR
Lutathera (Lu-177)	Therapeutic	1	amino acids	drug toxicity prophylaxis, neuroendocrine tumor	F (75)	11/1/2018	1/9/2019	N/A	extravasation, infusion site pain	non-serious	non-serious	Advanced Accelerator Applications	US
Lymphoseek (Tc-99m Tilmanocept)	Diagnostic	1	N/A	lymphatic mapping	M (82)	3/14/2018	4/23/2019	N/A	injection site haemorrhage, injection site pain, incorrect dose administered	non-serious	non-serious	Cardinal Health	US
Myoview (Tc-99m tetrofosmin)	Diagnostic	1	Sodium chloride	Ischaemic, cardiomyopathy, product used for unknown indication, scan myocardial perfusion	M (88)	1/16/2019	2/6/2019	N/A	extravasation	serious	other outcomes	Astellas	FR
Myoview (Tc-99m tetrofosmin)	Diagnostic	1	N/A	Diagnostic procedure, product used for unknown indication	NS	UNK	5/20/2016	N/A	extravasation	non-serious	non-serious	GE Healthcare	US
Myoview (Tc-99m tetrofosmin)	Diagnostic	1	TC-99m generator	Diagnostic procedure, product used for unknown indication	M	9/29/2016	2/1/2017	N/A	extravasation	non-serious	non-serious	GE Healthcare	US
Quadramet	Therapeutic	1	fentanyl, sodium chloride	prostate cancer	M	2004	5/31/2005	9/12/2012	extravasation, anaemia, incorrect route of product administration, injection site reaction, gastrointestinal haemorrhage	serious	hospitalized		
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	bone scan	F (24)	1/31/2002	2/12/2002	N/A	injection site erythema, injection site extravasation, pyrexia, toxicity to various agents, chills, injection site inflammation, injection site edema, cellulitis	serious	required intervention	submitted by Mallinckrodt	NS
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	bone scan	F (28)	2/22/2002	6/12/2003	N/A	extravasation, skin reaction	serious	other outcomes	submitted by Mallinckrodt	NS
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	radioisotope scan	F (52)	10/16/2003	11/10/2003	N/A	extravasation, injection site swelling, injection site erythema	serious	required intervention	submitted by Mallinckrodt	NS
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	bone scan	M (39)	9/30/2011	10/25/2011	11/8/2011	product administration error, injection site extravasation, injection site inflammation	serious	other outcomes	submitted by Covidien	NL
Technescan Hdp (oxidronate)	Diagnostic	1	zofran, zantac, deadron, potassium chloride, hydrochlorothiazide	bone scan, breast cancer metastatic, dyspepsia, edema, radioisotope scan	NS	10/19/2007	10/19/2007	10/23/2007	cellulitis, product administration error, injection site swelling, injection site extravasation, injection site erythema, injection site pain	serious	hospitalized	submitted by Covidien	US
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	bone scan	NS	4/1/2008	6/13/2008	6/13/2008	injection site cellulitis, injection site extravasation, product administration error	serious	other outcomes	submitted by Covidien	US
Technescan Hdp (oxidronate)	Diagnostic	1	N/A	bone scan	NS	11/16/2009	12/16/2009	12/16/2009	product administration error, phlebitis, extravasation	serious	other outcomes	submitted by Covidien	US
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scintigraphy	M (72)	UNK	N/A	7/16/2019	extravasation	UNK	unknown	EEA Regulator	NS
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scintigraphy	M (54)	UNK	N/A	12/4/2018	extravasation	Other	recovered/resolved	EEA Regulator	NS
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scan, joint inflammation	M (38)	UNK	N/A	3/26/2019	cold sweat, injection site extravasation, pain		recovered/resolved	Curium Pharmaceuticals	NL

Adverse Event and Vigilance Reports

Radiotracer	Diagnostic or Therapeutic?	# of Cases	Concomitant Product Names	Reason for Use	Sex and Age	Event Date	FDA Reported Date	EU Reported Date	Reaction(s)	Serious/Seriousness	Outcomes	Sender	Country where event occurred
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scintigraphy	F	UNK	N/A	12/10/2018	injection site extravasation	UNK	recovered/resolved	EEA Regulator	NS
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scan	M (55)	UNK	N/A	11/15/2012	injection site extravasation, injection site ulcer	Other	unknown	CIS BIO International	NS
Technetium 99m oxidronate	Diagnostic	1	N/A	Algoneurodystrophy	F (31)	UNK	N/A	4/4/2011	erysipelas, injection site extravasation, injection site inflammation	caused/prolonged hospitalization	recovered/resolved	CIS BIO International	NS
Technetium 99m oxidronate	Diagnostic	1	N/A	bone scan	M (32)	UNK	N/A	1/22/2010	injection site extravasation, edema, rash erythematous	disability	recovered/resolved	EEA Regulator	NS
Technescan MAG3 (mertiatide)	Diagnostic	1	N/A	renal scan	M (54 days	5/22/2019	6/27/2019	N/A	extravasation	non-serious	non-serious	Curium Pharmaceuticals	US
Technescan MAG3 (mertiatide)	Diagnostic	1	N/A	renal scan	F (0)	10/18/2010	6/22/2011	N/A	injection site extravasation, product administration error	non-serious	non-serious	Covidien	US
Technescan MAG3 (mertiatide)	Diagnostic	1	N/A	radioisotope scan, renal scan	NS	3/11/2008	7/22/2008	N/A	pain, injection site swelling, injection site pain, product administration error, swelling, injection site extravasation	non-serious	non-serious	Covidien	US
Technetium Tc-99m Etidronate	Diagnostic	1	N/A	UNK	M (81)	UNK	8/22/2011	N/A	peripheral edema, extravasation	non-serious	non-serious	N/A	N/A
Technetium TC-99m Medronate (MDP)	Diagnostic	1	evothyroxine, atorvastatii	blood cholesterol increased, diagnostic procedure, hypothyroidism, product used for unknown indication	F (64)	7/8/2014	8/29/2014	N/A	hypoaesthesia, paraesthesia, peripheral swelling, injection site extravasation, pain in extremity	serious	other outcomes	GE Healthcare	US
Technetium TC-99m Pentetate	Diagnostic	1	N/A	RI scan	M (67)	UNK	N/A	3/19/2018	injection site extravasation, injection site edema, injection site pain	Other	recovered/resolved	EEA Regulator	NS
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	stress echocardiogram	M (94)	9/6/2017	1/11/2018	N/A	injection site extravasation	non-serious	non-serious	Lantheus Medical Imaging	US
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	radioisotope scan	M (42)	7/15/2017	1/12/2017	N/A	infusion site extravasation, infusion site swelling	non-serious	non-serious	Lantheus Medical Imaging	US
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	product used for unknown indication	F	UNK	1/12/2017	N/A	product administration error	non-serious	non-serious	Lantheus Medical Imaging	US
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	product used for unknown indication	NS	UNK	1/13/2016	N/A	product administration error	non-serious	non-serious	Lantheus Medical Imaging	US
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	advair Hfa, flonase, spiriva, singular, naproxen	cardiac stress test	F (48)	7/1/2013	8/1/2013	8/1/2013	retching, feeling hot, vomiting, nausea, loss of consciousness, seizure, cardiac arrest, infusion site extravasation, presyncope, abdominal pain, electrocardiogram St segment depression	serious	other outcomes, life threatening	Lantheus Medical Imaging	NS
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	UNK	F	UNK	1/10/2008	N/A	pain, injection site extravasation, ecchymosis	non-serious	non-serious	Bristol Myers Squibb	US
Technetium Tc-99m Sestamibi (Cardiolite)	Diagnostic	1	N/A	UNK	F	UNK	9/19/2001	N/A	discomfort, necrosis, peripheral nerve injury, injection site extravasation	serious	other outcomes	Dupont	NS
Technetium Tc-99m Sestamibi	Diagnostic	1	N/A	UNK	F	UNK	N/A	5/24/2019	extravasation, swelling	UNK	unknown	EEA Regulator	NS
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	metastases to bone, prostate cancer stage Iv	M (81)	UNK	10/2/2018	10/2/2018	extravasation, infusion site extravasation	serious	other outcomes	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	prostate cancer	M	UNK	5/3/2018	N/A	incorrect dosage administered, administration site extravasation	non-serious	non-serious	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	prostate cancer stage Iv	M	UNK	5/7/2018	N/A	injection site extravasation	non-serious	non-serious	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	metastases to bone, prostate cancer stage Iv	M (61)	UNK	11/20/2014	3/13/2017	squamous cell carcinoma of skin, administration site extravasation	serious	other outcomes	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	UNK	NS	UNK	1/11/2017	N/A	extravasation	non-serious	non-serious	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	UNK	M	11/5/2015	11/18/2015	12/18/2015	infusion site extravasation	serious	other outcomes	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	prostate cancer metastatic	M (79)	7/2/2014	7/8/2014	7/22/2014	incorrect dose administered, infusion site extravasation	serious	other outcomes	Bayer	US
Xofigo (Radium RA-223 dichloride)	Therapeutic	1	N/A	UNK	M	UNK	N/A	3/12/2018	extravasation	UNK	unknown	Bayer	NS

Adverse Event and Vigilance Reports

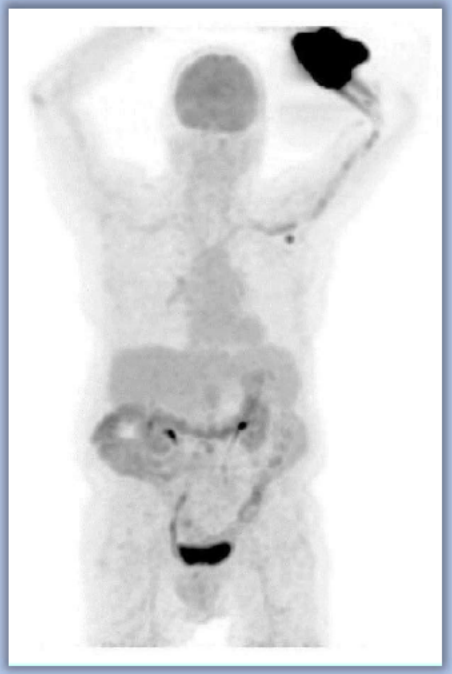
Radiotracer	Diagnostic or Therapeutic?	# of Cases	Concomitant Product Names	Reason for Use	Sex and Age	Event Date	FDA Reported Date	EU Reported Date	Reaction(s)	Serious/Seriousness	Outcomes	Sender	Country where event occurred
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	Rituxan (MabThera)	non-Hodgkin's Lymphoma	M (65)	2/1/2008	11/6/2008	N/A	Infusion site ulcer, feeling hot, skin necrosis, skin exfoliation, erythema, pain, infusion site extravasation	serious	other outcomes	Cell Therapeutics	NS
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	senokot, lactulose, allopurinol, coumadin	non-Hodgkin's Lymphoma	M (64)	UNK	4/28/2005	N/A	Blood lactate dehydrogenase increased, radiation skin injury, extravasation, malignant	serious	died	Biogen	NS
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	cytarabine, MabThera, Etoposide, melphalan	mantle cell lymphoma stage IV	M	UNK	N/A	6/11/2018	erythema, extravasation, injection site reaction, joint range of motion decrease, off label use, pain, radiation injury, radiation skin injury, skin necrosis, skin swelling	caused/prolonged hospitalization	recovering/resolving	EEA Regulator	NS
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	N/A	non-Hodgkin's Lymphoma	M (64)	UNK	N/A	11/24/2008	infusion site extravasation, skin ulcer, injection site necrosis	other	recovered/resolved	EEA Regulator	NS
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	MebThera, Indium	non-Hodgkin's Lymphoma	F (80)	UNK	N/A	3/22/2007	infusion site extravasation	other	unknown	Bayer Pharma AG	NS
Zevalin (Yttrium-90 ibritumomab tiuxetan)	Therapeutic	1	MebThera, Indium	non-Hodgkin's Lymphoma	M (83)	UNK	N/A	7/2/2008	injection site extravasation	Other	recovered/resolved	Bayer AG	NS

Attachment 3: Extravasation Equivalent Dose Analyses

Attachment 3, Case 1

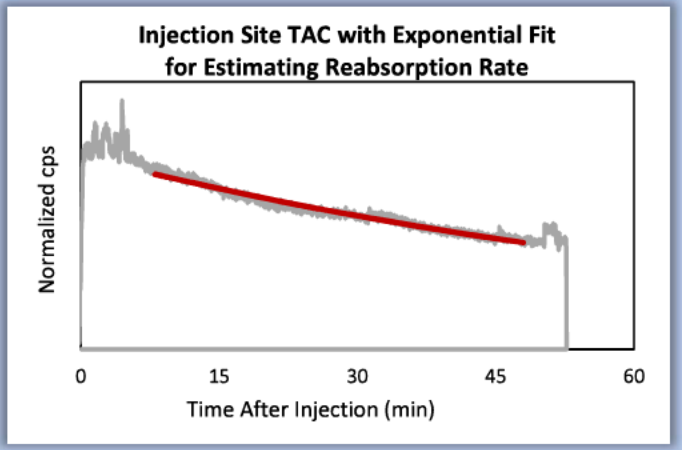
Scan #14547

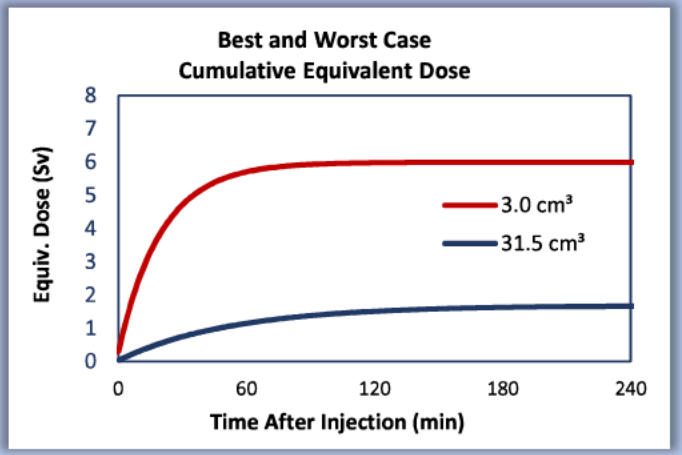
Equivalent Dose: 1.7 to 6.0 Sv



Radioisotope:	F-18
Physical Half-life	109.77 min
Injection Method	Manual
Injection Location:	L Forearm
Injected Activity:	10.2 mCi
Radiotracer Volume	1.5 mL
Saline Flush Volume	30 mL
Imaging Time:	62 min
% Infiltration:	100 %
Initial Activity	10.2 mCi
Imaging Time Activity	5.2 mCi
Reabsorption Rate (half-life):	55.9 min

Dose Calculation Volume	3.0 to 31.5 cm³
Dose Rate	3.1 to 28.5 mSv/mCi-min
Total Equivalent Dose	1.7 to 6.0 Sv





The patient was injected in the left forearm with 10.2 mCi of FDG. Lucerno's Lara® System identified the presence of excess radiotracer near the injection site.

The patient had a repeat scan the next day. Axial images of a pancreatic tumor revealed the infiltration caused the original SUVs to be understated by 65%.

Using PET-measured infiltration activity at imaging time and the time-activity curve data, we estimate that 100% of the injected activity was infiltrated. We calculated equivalent dose based on initial tissue volumes ranging from 3.0 to 31.5 cm³.

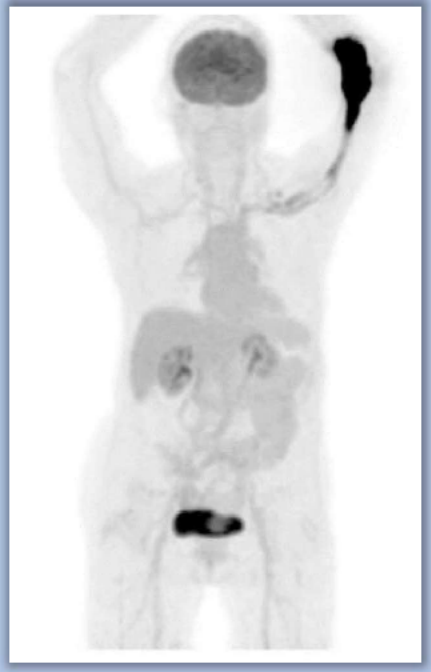
In addition to the negative effect that this infiltration had on the patient's diagnostic study, the patient also received between 1.7 and 6.0 Sv of equivalent dose to their forearm tissue.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume with a minimum volume of 1 cm³.
- Initial Infiltration amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled as a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 2

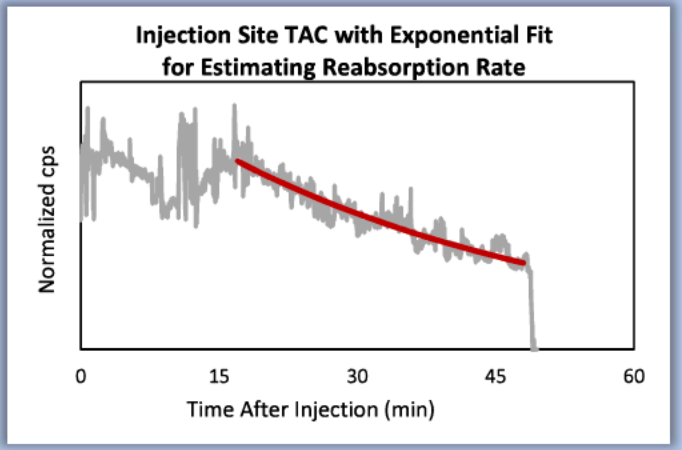
Scan #15170

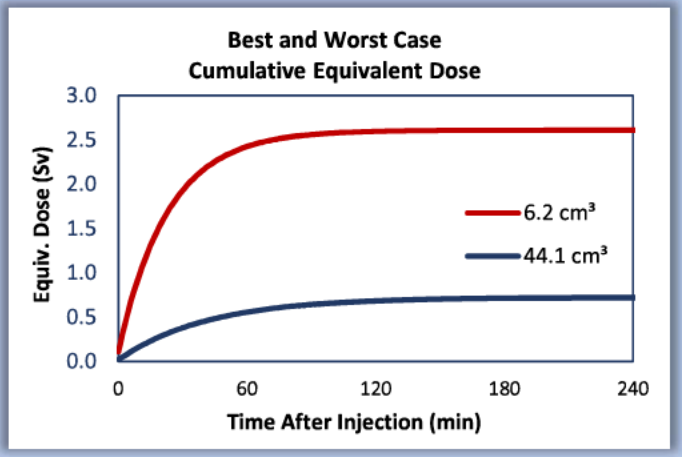
Equivalent Dose: 0.7 to 2.6 Sv



Radioisotope:	F-18
Physical Half-life	109.77 min
Injection Method	Auto
Injection Location:	Left AC
Injected Activity:	10.0 mCi
Radiotracer Volume	4.0 mL
Saline Flush Volume	41.0 mL
Imaging Time:	62 min
% Infiltration:	77 %
Initial Activity	7.7 mCi
Imaging Time Activity	1.6 mCi
Reabsorption Rate (half-life):	27.6 min

Dose Calculation Volume	6.2 to 44.1 cm³
Dose Rate	2.2 to 14.4 mSv/mCi-min
Total Equivalent Dose	0.7 to 2.6 Sv





As part of a breast tumor assessment study, the patient was injected in the left antecubital with 10.0 mCi of FDG using an auto-injector. Lucerno's Lara® System identified the presence of excess radiotracer near the injection site even though the auto-injector reported an error-free injection.

This patient had a repeat scan three days later. The repeat PET scan revealed the infiltration caused the SUVs of a breast tumor to be understated by 73%. An assessment based on the infiltrated scan would have erroneously concluded that the disease was responding favorably to the treatment regimen. A revised assessment based on the repeat study showed the disease was recalcitrant.

Using PET-measured infiltration activity at imaging time and the time-activity curve data, we estimated that 77% of the injected activity was infiltrated. We calculated equivalent dose based on tissue volumes ranging from 6.2 to 44.1 cm³.

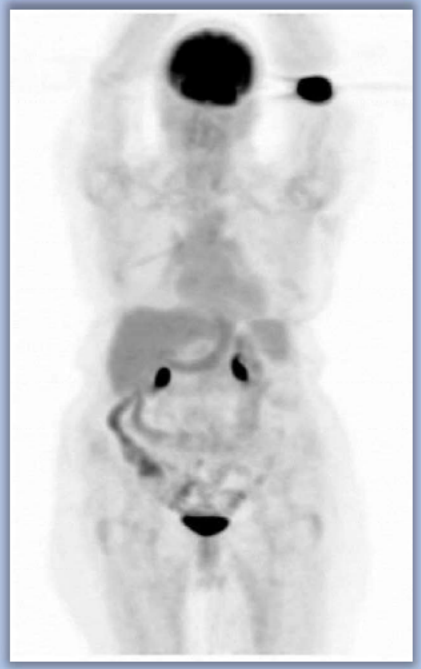
In addition to the negative effect that this infiltration had on the patient's assessment study, the patient also received between 0.7 and 2.6 Sv of equivalent dose to their arm tissue.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume with a minimum volume of 1 cm³.
- Initial Infiltration amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled as a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 3

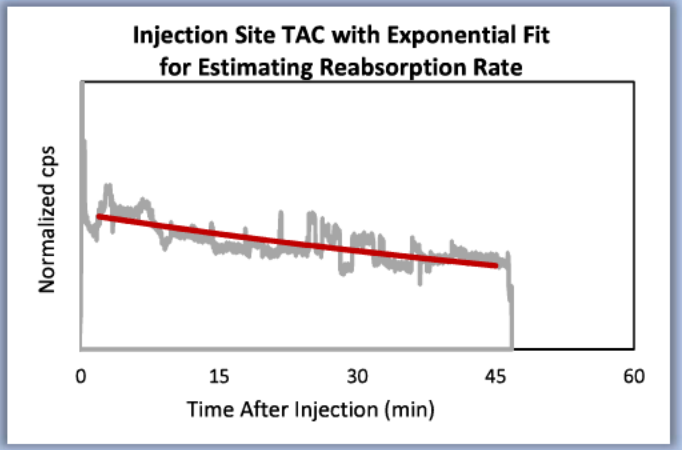
Scan #16074

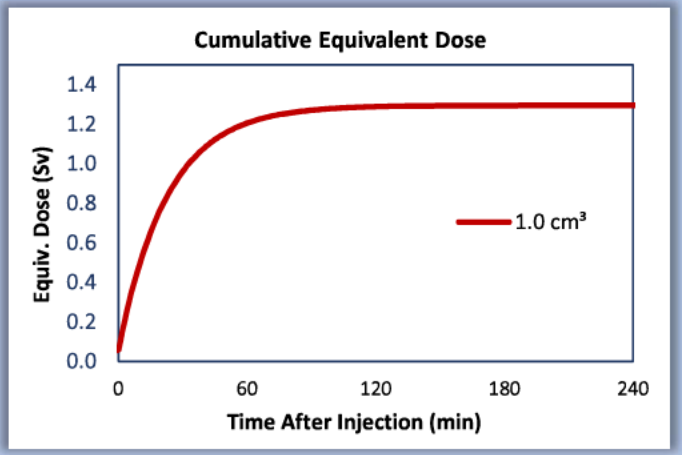
Equivalent Dose: 1.3 Sv



Radioisotope:	F-18
Physical Half-life	109.77 min
Injection Method	Manual
Injection Location:	Left AC
Injected Activity:	17.7 mCi
Radiotracer Volume	2.6 mL
Saline Flush Volume	0.0 mL
Imaging Time:	67 min
% Infiltration:	4 %
Initial Activity	0.7 mCi
Imaging Time Activity	0.3 mCi
Reabsorption Rate (half-life):	64.7 min

Dose Calculation Volume	1.0 cm³
Dose Rate	80.5 mSv/mCi-min
Total Equivalent Dose	1.3 Sv





The patient was injected in the left antecubital with 17.7 mCi of FDG. The technologist performing the injection reported that the patient complained of pain near the IV after the radiotracer injection. As such, the technologist did not flush with saline.

No repeat of the imaging study was ordered in response to this infiltrated injection.

Using PET-measured infiltration activity at imaging time and the time-activity curve data, we estimate that 4% of the injected activity was infiltrated.

Because there was no saline flush, the infiltrated volume would be quite small, resulting in high calculated dose. Thus, we used 1 cm³ as a minimum initial infiltrated volume.

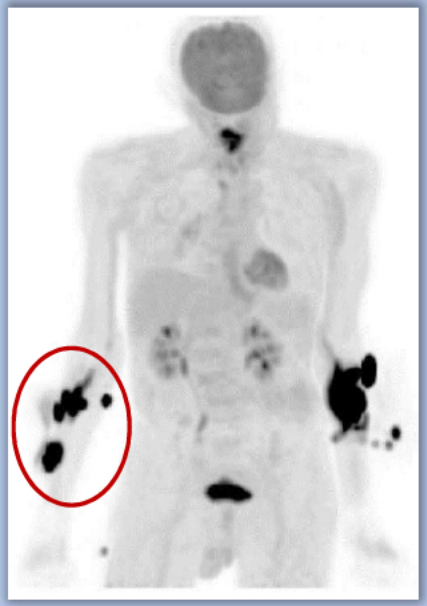
We estimate that 1 cm³ of the patient's arm tissue received an unintended equivalent dose exposure of 1.3 Sv.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume with a minimum volume of 1 cm³.
- Initial Infiltration amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled as a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 4

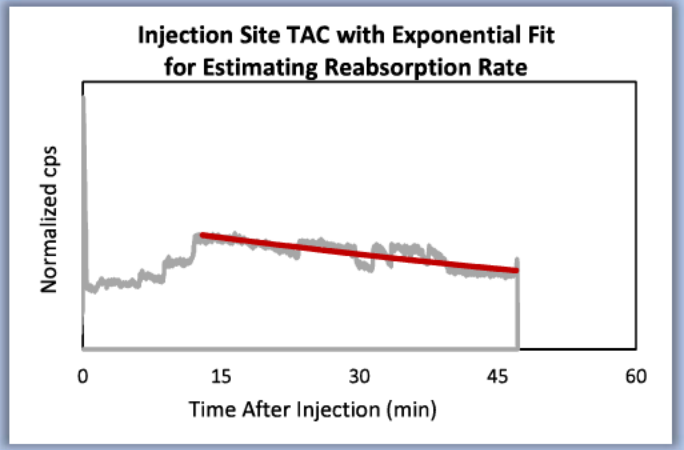
Scan #16031R

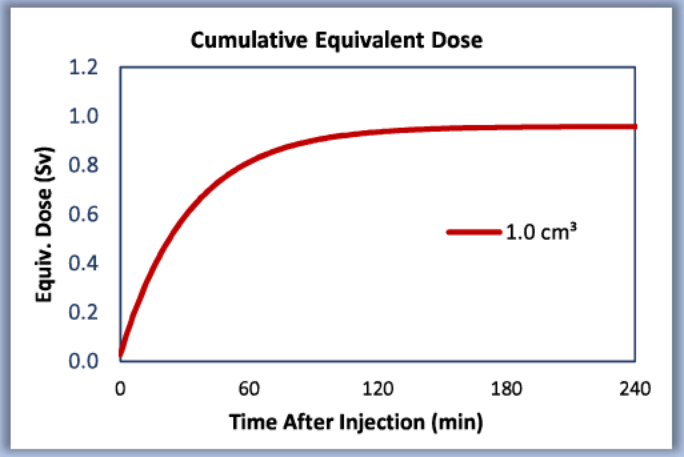
Equivalent Dose: 1.0 Sv



Radioisotope:	F-18
Physical Half-life	109.77 min
Injection Method	Manual
Injection Location:	Right AC
Injected Activity:	4.8 mCi
Radiotracer Volume	0.9 mL
Saline Flush Volume	0.0 mL
Imaging Time:	56 min
% Infiltration:	7 %
Initial Activity	0.4 mCi
Imaging Time Activity	0.2 mCi
Reabsorption Rate (half-life):	63.5 min

Dose Calculation Volume	1.0 cm^3
Dose Rate	80.5 mSv/mCi-min
Total Equivalent Dose	1.0 Sv





In the course of their PET scan, this patient was injected twice and both injections were infiltrated. The technologist performing the injection reported that they tried to inject in the right antecubital and realized an infiltration was occurring. He withdrew the catheter and started another IV in the left antecubital to finish the procedure.

For our analysis, we assume half of the radiotracer was injected into each arm.

In the first attempt, 4.8 mCi of FDG was injected into the patient's right antecubital and was not flushed. Using PET-measured infiltration activity at imaging time and the time-activity curve data, we estimated that 7% of the 4.8 mCi was infiltrated. We used 1 cm^3 for the initial infiltrated tissue volume.

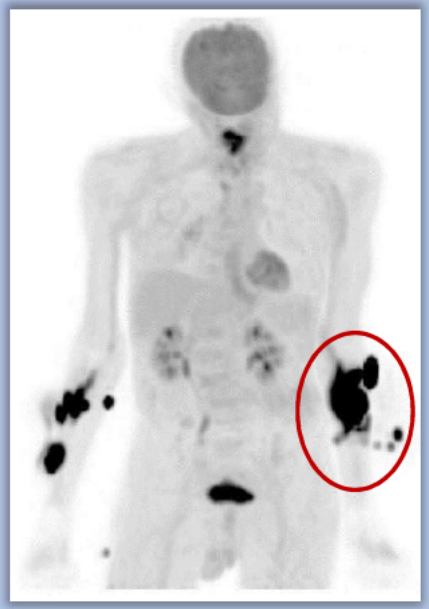
From this first injection, 1 cm^3 of the patient's arm tissue received unintended equivalent dose of 1.0 Sv.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume with a minimum volume of 1 cm^3.
- Initial Infiltration amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled as a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 5

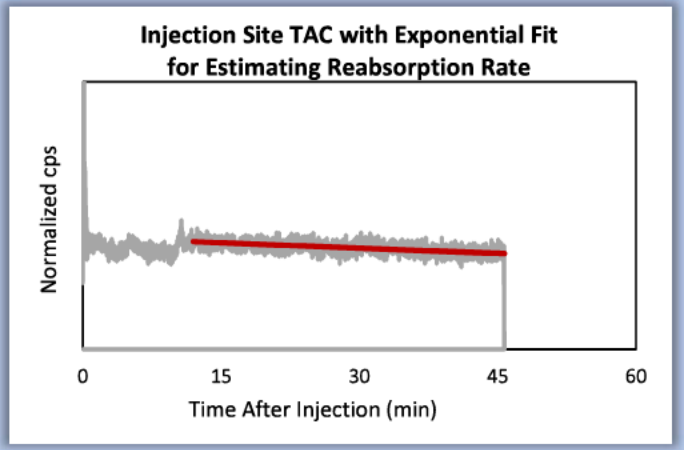
Scan #16031L

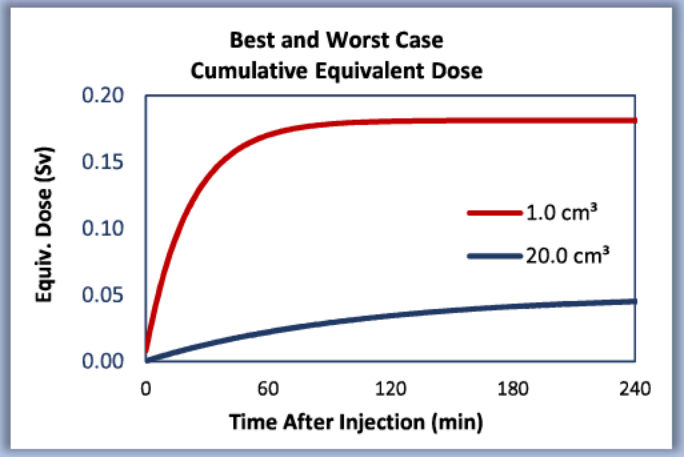
Equivalent Dose: 0.05 to 0.18 Sv



Radioisotope:	F-18
Physical Half-life	109.77 min
Injection Method	Manual
Injection Location:	Left AC
Injected Activity:	4.8 mCi
Radiotracer Volume	0.9 mL
Saline Flush Volume	20 mL
Imaging Time:	56 min
% Infiltration:	2 %
Initial Activity	0.10 mCi
Imaging Time Activity	0.08 mCi
Reabsorption Rate (half-life):	197.5 min

Dose Calculation Volume	1.0 to 20.0 cm³
Dose Rate	4.7 to 80.5 mSv/mCi-min
Total Equivalent Dose	0.05 to 0.18 Sv





In the course of their PET scan, this patient was injected twice and both injections were infiltrated. The technologist performing the injection reported that they tried to inject in the right antecubital and realized an infiltration was occurring. He withdrew the catheter and started another IV in the left antecubital to finish the procedure.

For our analysis, we assume half of the radiotracer was injected into each arm.

In the second attempt, 4.8 mCi of FDG was injected into the patient's left antecubital and flushed with 20 mL of saline. Using PET-measured infiltration activity at imaging time and the time-activity curve data, we estimated that 2% of the injected activity was infiltrated. We calculated equivalent dose based on tissue volumes ranging from 1.0 to 20.0 cm³.

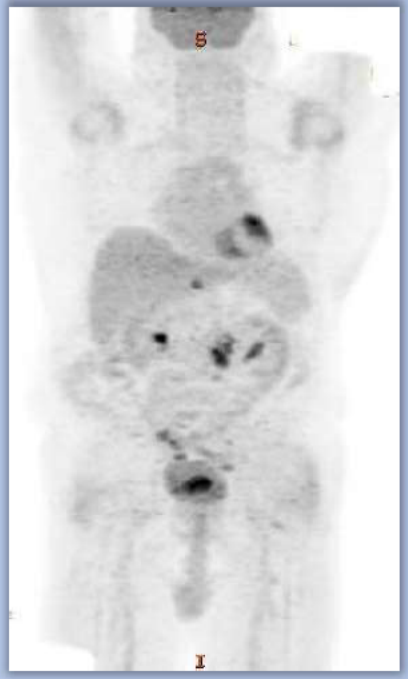
From this second injection, the patient's arm tissue received unintended equivalent dose of between 0.05 and 0.18 Sv.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume with a minimum volume of 1 cm³.
- Initial Infiltration amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled as a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 6

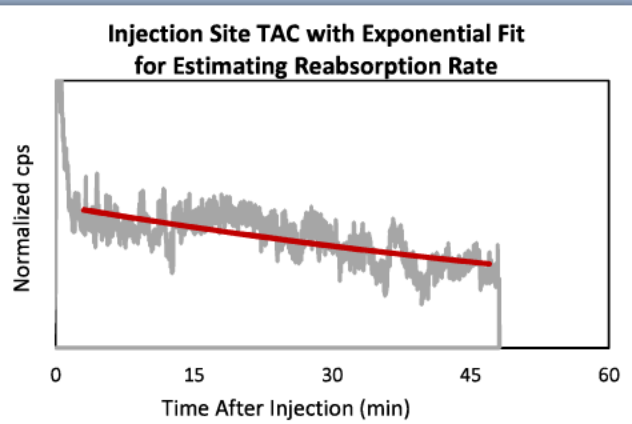
Scan #11490

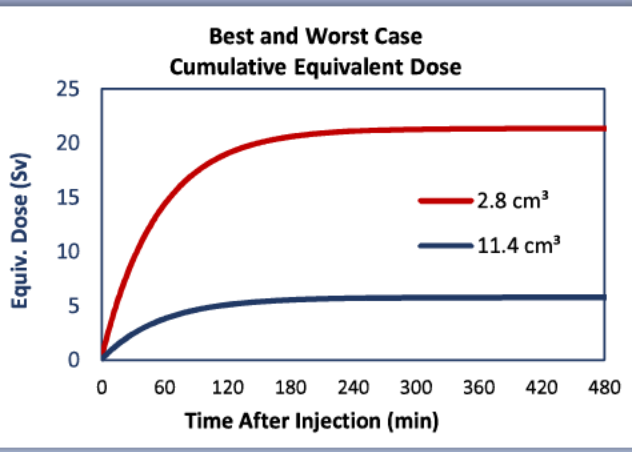
Equivalent Dose: 5.8 to 21.4 Sv



Radioisotope:	F-18
Physical Half-life	109.8 min
Injection Method	Manual
Injection Location:	Left Hand
Injected Activity:	13.7 mCi
Radiotracer Volume	1.5 mL
Saline Flush Volume	10.0 mL
Imaging Time:	57 min
% Infiltration:	92 %
Initial Activity	12.6 mCi
Imaging Time Activity	4.6 mCi
Reabsorption Rate (half-life):	61.4 min

Dose Calculation Volume	2.8 to 11.4 cm^3
Dose Rate	8.1 to 30.8 mSv/mCi-min
Total Equivalent Dose	5.8 to 21.4 Sv





The patient was injected in the left hand with 13.7 mCi of FDG. The injection site was out of the PET imaging field of view. Had Lucerno's Lara® System not identified the presence of excess radiotracer near the injection site, no one would have known that the patient had been infiltrated.

This patient had a repeat scan five days later, and four lesions were studied. The new data showed that the infiltration caused the original SUVs to be understated by 33-54%, and MTV calculations were understated by 32-70%. Using the infiltrated image would likely have impacted patient care.

Using the change in quantifiable measures as an indicator of infiltration severity, we estimated that approximately 92% of the injected activity was infiltrated. We calculated equivalent dose based on initial tissue volumes ranging from 2.8 to 11.4 cm^3.

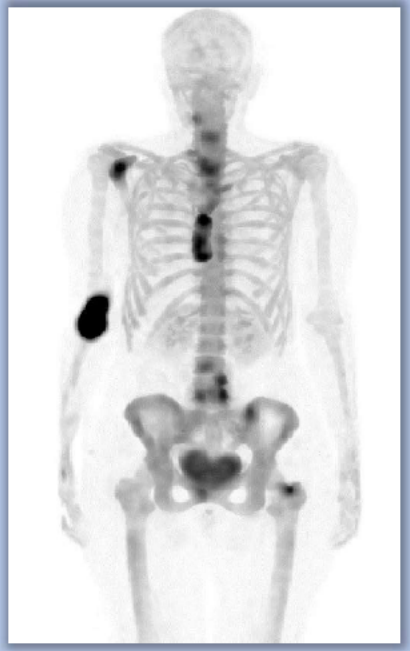
In addition to the negative effect that this infiltration had on the patient's diagnostic study, the patient also received between 5.8 and 21.4 Sv of unintended exposure to their hand tissue.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume. Volume is not allowed to be less than 1 cm^3.
- Reabsorption rate estimates are based on injection site monitoring data from Lara® sensors.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 7

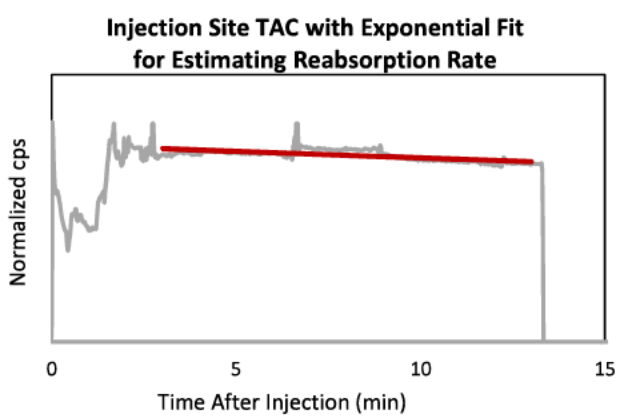
Scan #15771

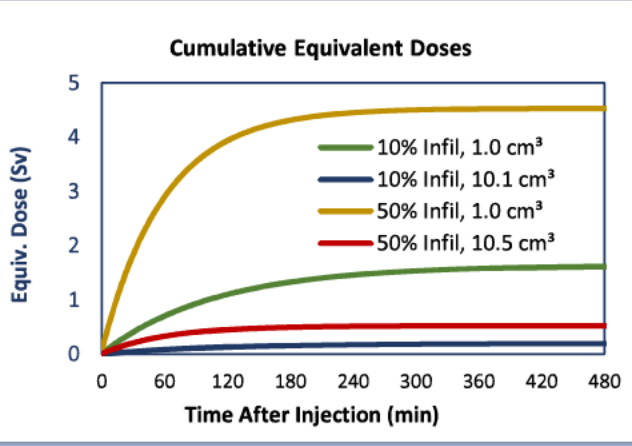
Equivalent Dose: 0.2 to 4.5 Sv



Radioisotope:	Tc-99m	
Physical Half-life	360.4	min
Injection Method	Manual	
Injection Location:	Right AC	
Injected Activity:	25.38	mCi
Radiotracer Volume	1.0	mL
Saline Flush Volume	10.0	mL
Imaging Time:	214	min
% Infiltration:	10 to 50	%
Initial Activity	2.5 to 12.7	mCi
Imaging Time Activity	0.4 to 1.9	mCi
Reabsorption Rate (half-life):	100.5	min

Dose Calculation Volume	1.0 to 10.5	cm^3
Dose Rate	0.7 to 5.9	mSv/mCi-min
Total Equivalent Dose	0.2 to 4.5	Sv





For a therapy assessment scan, the patient was injected in the right antecubital with 25.4 mCi of Tc-99m. Lucerno's Lara® System identified the presence of excess radiotracer near the injection site.

No repeat of the imaging study was ordered in response to this infiltrated injection.

No activity quantification could be made from the SPECT images, but infiltrated tissue volume was measured. Time-activity curve data was used to estimate the rate of reabsorption.

Equivalent dose was calculated for initial infiltrations ranging from 10% to 50% with corresponding initial tissue volumes of 1.0 to 10.1 cm^3 for 10% and 1.0 to 10.5 cm^3 for 50%.

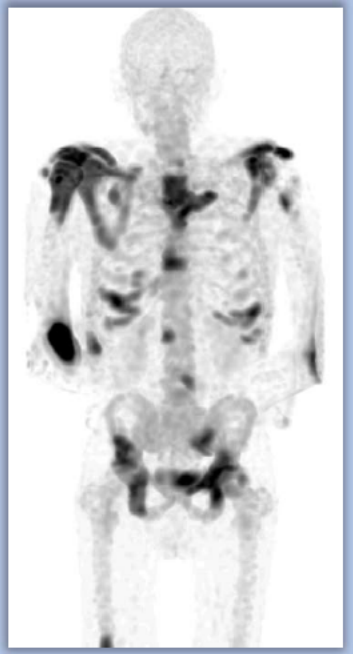
The patient's arm tissue was exposed to unintended equivalent dose between 0.2 and 4.5 Sv.

- Dose Calculation Volume is twice the infiltrated radiotracer volume or the total flush volume plus the infiltrated radiotracer volume. Volume is not allowed to be less than 1 cm^3.
- Reabsorption rate estimates are based on injection site monitoring data from Lara® sensors.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Attachment 3, Case 8

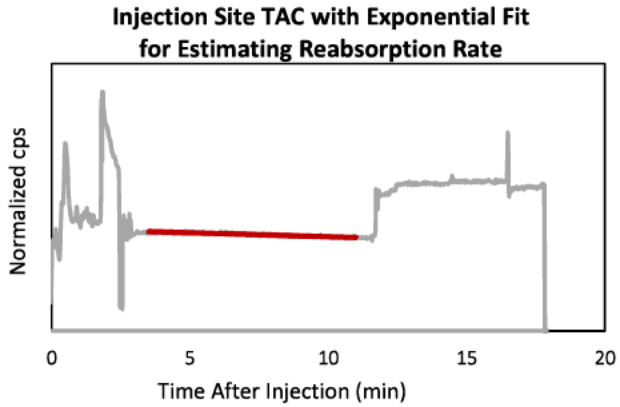
Scan #15819

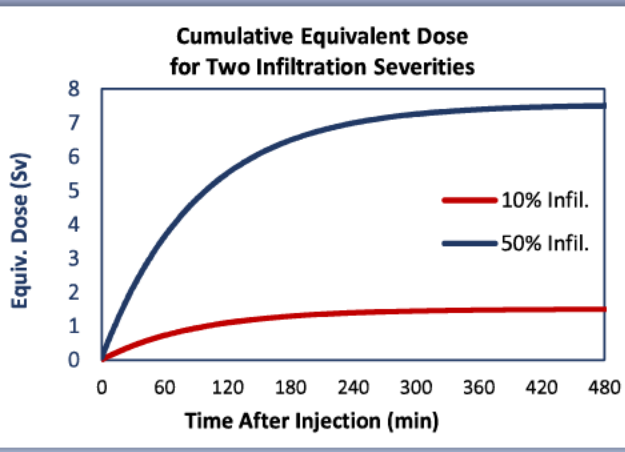
Equivalent Dose: 1.5 to 7.5 Sv



Radioisotope:	Tc-99m	
Physical Half-life	360.4	min
Injection Method	Manual	
Injection Location:	Right AC	
Injected Activity:	27.4	mCi
Radiotracer Volume	1.5	mL
Saline Flush Volume	0.0	mL
Imaging Time:	247	min
% Infiltration:	10 to 50	%
Initial Activity	2.7 to 13.7	mCi
Imaging Time Activity	0.2 to 1.0	mCi
Reabsorption Rate (half-life):	81.7	min

Dose Calculation Volume	1.0	cm^3
Dose Rate	5.9	mSv/mCi-min
Total Equivalent Dose	1.5 to 7.5	Sv





For a bone scan, the patient was injected in the right antecubital with 27.4 mCi of Tc-99m. Lucerno's Lara® System identified the presence of excess radiotracer near the injection site.

No repeat of the imaging study was ordered in response to this infiltrated injection.

No activity quantification could be made from the SPECT images, but infiltrated tissue volume was measured. Time-activity curve data was used to estimate the rate of reabsorption.

This injection was a "straight stick" procedure with no saline flush after the radiotracer injection. When no flush is performed, initial infiltration volumes are very small. We have used 1 cm^3 as the initial infiltrated tissue volume to avoid excessively high estimates of dose for a very small volume.

Equivalent dose was calculated for initial infiltrations ranging from 10% to 50%. The patient's arm tissue was exposed to unintended equivalent dose between 1.5 and 7.5 Sv.

- Dose Calculation Volume is assumed to be 1 cm^3 because injected volume is small.
- Reabsorption rate estimates are based on injection site monitoring data from Lara® sensors.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.