

## A Forum on Extravasation in Nuclear Medicine

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### INTRODUCTION

IN THE context of clinical medicine, extravasation is defined as the unintentional leakage of intravenous (IV) fluids or medications from a vein into the surrounding tissue. This event generally results from the tip of the IV catheter causing a hole in a vein wall. Unintentional extravasation of IV fluids is reported to be reasonably frequent, occurring in up to 6-10% of conventional IV administrations. If the IV solution is saline, this is generally not a serious issue. However, for example, if the IV solution is a chemotherapeutic agent, there can be significant local tissue damage and subsequent morbidity.

When extravasation occurs in administration of a radiopharmaceutical, then a different problem occurs. There is leakage of radioactive material into the interstitial space, generally in the arm. If dosimetry is performed, the source activity and geometry are usually complex and unknown. However, the half-life of radiopharmaceuticals is generally short, which is a mitigating factor for dose considerations.

In May 2020, Lucerno Dynamics, LLC, requested the US Nuclear Regulatory Commission (NRC) revise its medical event reporting regulations to require the reporting of extravasations that exceed 0.5 Sv dose equivalent to tissue. The NRC subsequently requested public comment whether extravasation of radiopharmaceuticals should be classified as a medical event (Docket: NRC-2020-0141; Nuclear Medicine Injection Extravasations as Medical Events). Under the auspices of Health Physics Society (HPS) Past President Eric Golden, Craig Little, as a representative of the HPS, provided comment. This submission in summary noted that the purpose of reporting medical events was for the NRC to evaluate

if there is a breakdown in the licensee's program or if there was a generic issue that should be reported to other licensees. The HPS comments acknowledge that extravasation frequently occurs in normal intravenous procedures and that it is almost impossible to prevent. Such events are therefore inconsistent with the stated purpose of a Medical Event. HPS further noted that, where feasible, the dose to surrounding tissue should be estimated but that a specific dose determination may not have a significant impact on clinical patient management.

The HPS has been asked to withdraw its comments, which current HPS President John Cardarelli has declined to do. The HPS position is that our submission is based on sound science and represents a consistent position along with several other scientific organizations. However, in an effort to improve communication within and among the scientific community, various organizations have been invited to submit concerns to a *Health Physics* Forum on Extravasation in Nuclear Medicine.

The correspondence in this special submission to *Health Physics* includes the HPS comments on extravasation as a medical event as well as opposing views from former HPS President Darrell Fisher, Lucerno Dynamics, Patients for a Safer Nuclear Medicine (PSNM), and a consortium of comments moderated by David Townsend. These comments have not been peer-reviewed by the Journal and are presented as submitted. The HPS is pleased to provide this venue where concerns can be published in a scientific journal. We believe a transparent discussion will strengthen the scientific exchange regarding the issue of extravasation.



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<sup>1</sup>Associate Editor, *Health Physics*.

The author declares no conflicts of interest.

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# HEALTH PHYSICS SOCIETY

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*Specialists in Radiation Safety*

October 14, 2020

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**Eric Goldin, Ph.D., CHP**  
President

Subject: Docket ID [NRC-2020-0141](#) - Reporting Nuclear Medicine Injection Extravasations as Medical Events

The Health Physics Society<sup>1</sup> (HPS) is a professional organization whose mission is to promote excellence in the science and practice of radiation safety. The HPS appreciates the opportunity to provide comments, in the attached document, as a response to the September 15, 2020 request.

If you have any questions regarding these comments, please contact the HPS Agency Liaison, Craig Little, at 970-260-2810 or by email to [agencyliaison@hps.org](mailto:agencyliaison@hps.org).

Sincerely,

Eric Goldin, PhD, CHP  
President

cc: Craig Little, PhD, HPS Agency Liaison  
Brett Burk, HPS Executive Director

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<sup>1</sup> The Health Physics Society is a non-profit scientific professional organization whose mission is to promote the practice of radiation safety. Since its formation in 1956, the Society has grown to include over 4,000 scientists, physicians, engineers, lawyers, and other professionals representing academia, industry, government, national laboratories, the Department of Defense, and other organizations. Society activities include encouraging research in radiation science, developing standards, and disseminating radiation safety information. Society members are involved in understanding, evaluating, and controlling the potential risks from radiation relative to the benefits. Official position statements are prepared and adopted in accordance with standard policies and procedures of the Society.

## Health Physics Society Comments on Reporting Nuclear Medicine Injection Extravasations as Medical Events

### Position Details

As a scientific organization of professionals who specialize in radiation safety, the HPS does not believe the infiltration/extravasation of radiopharmaceuticals should be classified as a Medical Event. Infiltration of a portion of the radiopharmaceutical is often unavoidable, and in the case of sentinel node imaging, is even intentional. Labeling an infiltration as a Medical Event carries a fairly serious stigma, and yet there is no evidence that infiltration of radiopharmaceuticals carries any health consequences for the patient or the general public.

As detailed in the NRC's Advisory Committee on Medical Use of Isotopes (ACMUI)<sup>2</sup>, the purpose of reporting Medical Events was for the NRC to evaluate if there is a breakdown in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the Authorized User (AU), or if there was a generic issue that should be reported to other licensees, that could lead to reduced likelihood of other medical events and enhanced radiological safety. The report acknowledges that extravasation frequently occur in normal intravenous procedures and are almost impossible to prevent. Such events are inconsistent with the stated purpose of a Medical Event.

If NRC considers extravasation a Medical Event, such a classification could force the estimation of the localized dose. Accurate measurement may require serial CT imaging of the site, which may result in additional patient dose simply for the purpose of complying with a regulation. This additional imaging would add substantially to the costs of doing any procedure, including facility, technologist, and physician time. Additional documentation of the survey and measurement of infiltration would need to be included in the medical record, adding further to additional burden and raising the issue of needlessly alarming patients.

We note that the skin has a relatively low stochastic radiation risk, with a weighting factor of only 0.01 in the ICRP 103 methodology. It is our opinion that attributable stochastic risk from an infiltration is relatively unimportant in the context of the patient's radiation exposure from other diagnostic or therapeutic exposures. The focus for intervention and patient safety should be on the potential tissue reaction aspects of these incidents. In this context, more appropriate triggers for whether a Medical Event occurred than the use of the 0.5 Sv (50 rem) Medical Event limit should apply. For example, transient erythema from fluoroscopic x-rays is thought to have a relative threshold of 2 Gy (200 rad), with higher dose leading to increased injury. The Conference of Radiation Control Program Directors (CRCPD) recommends guidance for managing fluoroscopy skin doses in [PART F MEDICAL DIAGNOSTIC AND INTERVENTIONAL X-RAY AND IMAGING SYSTEMS](#). The suggested state regulations use the guidance of the American

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<sup>2</sup> Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasation, Final Report. April 6, 2020.

College of Radiology Technical Standard on managing radiation exposure in fluoroscopic procedures<sup>3</sup>. This technical standard recommends monitoring for and medically managing possible radiation effects when the dose reaches 5 Gy at the interventional reference point, a value approximating a 2 Gy skin dose

Patients routinely undergo procedures that entail potentially much higher than 0.5 Sv (50 rem) doses to skin in fluoroscopy procedures, which may or may not be optimized or tracked, and for which the consensus is that the dose to this tissue is not risk significant with respect to stochastic effects when considered in the context that includes the patient's dose from the rest of their care. When skin effects are seen (> 2 Gy) with escalating potential injury at higher doses), they are medically managed. This practice is consistent with the ICRP principles of justification and optimization.

We believe that continued close attention should be paid to avoid infiltration of ALL parenterally administered radiopharmaceuticals. We also acknowledge the specific concerns associated with the infusion of therapeutic agents and that extravasation of a therapeutic dosage of a radiopharmaceutical can result in potentially injurious radiation exposure to localized tissue. Oversight of therapy effects should also be considered in the context of the patient's care and may be more appropriately managed skin effects are in complex fluoroscopy cases<sup>4</sup>. Where feasible the dose should be estimated, but it should be recognized that there may be substantial barriers to doing so and that a specific dose determination may not have a significant impact on clinical management. In any case, appropriate medical intervention should be undertaken and that such incidents should be reported to the Radiation Safety Officer, Radiation Safety Committee and to the appropriate patient safety organization. It is unclear whether classifying infiltrations / extravasations, incidents which may be unavoidable, as a Medical Event best serves the interest of health and safety.

Response to specific questions:

**NRC question:** *How frequently does radiopharmaceutical extravasation occur?*

Extravasation is estimated to occur in 0.6% to 6% of radiopharmaceutical administrations<sup>5,6</sup>. In nuclear medicine however, there appear to be relatively few reports of side effects from extravasation of radiotherapeutic agents, and no reports of side effects related to extravasation of diagnostic agents (with regard to localized radiation dose)<sup>7</sup>.

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<sup>3</sup> American College of Radiology. ACR-AAPM [Technical Standard](#) for Management of the Use of Radiation in Fluoroscopic Procedures.

<sup>4</sup> The Joint Commission. Sentinel Event Alert 47: Radiation risks of diagnostic imaging and fluoroscopy. August 24, 2011. Revised February 2019.

<sup>5</sup> van der Pol J, Vöö S, Bucerius J, Mottaghy, F. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. *Eur J Nucl Med Mol Imaging* (2017) 44:1234–1243.

<sup>6</sup> Jordan K, Grothe W, Schmoll HJ. Extravasation of chemotherapeutic agents: prevention and therapy. *Dtsch Med Wochenschr.* 2005;130:33–37.

<sup>7</sup> Rhymer S, Parker JA, and Matthew R. Palmer M. Detection of 90Y Extravasation by Bremsstrahlung

**NRC question:** *For medical use licensees, does your facility currently monitor for radiopharmaceutical extravasation? If so, why and how do you monitor? If not, why not?*

Nuclear medicine clinics currently monitor for radiopharmaceutical extravasation. To reduce the risk of extravasation many clinics administer radiopharmaceuticals through an IV-catheter that has been test flushed to ensure patency while visually inspecting if swelling occurs and asking the patient if they experience discomfort during injection<sup>8</sup>. However, even with such precautions an extravasation may not be identified until the patient is imaged<sup>9</sup>.

**NRC question:** *Do you expect that monitoring for extravasation and reviewing the results would improve radiopharmaceutical administration techniques at medical use licensee facilities? If so, how? If not, why not?*

The techniques identified above reduce the number of extravasations during administration and existing reporting to the hospital quality assurance programs already provide oversight of the number of extravasations. Extravasations in nuclear medicine administrations are low in comparison to chemotherapy administrations, where the extravasation rate may be as high as 35 to 50%<sup>10</sup>.

As stated by NRC's Advisory Committee on the Medical Use of Isotopes (ACMUI), "The prevention of extravasation is a medical training issue for the authorized user (AU) physician and the technologist under the supervision of the AU, which is considered medical practice and not something that needs NRC regulation."<sup>11</sup>

Adding NRC oversight of extravasations will increase the regulatory burden without a radiological or patient safety benefit.

**NRC question:** *Do you believe an NRC regulatory action requiring monitoring and review of extravasation would improve patient radiological health and safety? If so, how? If not, why not?*

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Imaging for Patients Undergoing <sup>90</sup>Y-Ibritumomab Tiuxetan Therapy. J Nucl Med Technol 2010; 38:195–198.

<sup>8</sup> van der Pol J, Vöö S, Bucerius J, Mottaghy, F. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. Eur J Nucl Med Mol Imaging (2017) 44:1234–1243.

<sup>9</sup> Qutbi M. Masking Effect of Radiopharmaceutical Dose Extravasation During Injection on Myocardial Perfusion Defects During SPECT Myocardial Perfusion Imaging: A Potential Source of False Negative Result. Mol Imaging Radionucl Ther 2018;27:141-143.

<sup>10</sup> Nickel B. Peripheral Intravenous Access: Applying Infusion Therapy Standards of Practice to Improve Patient Safety. Crit Care Nurse 2019 Feb;39(1):61-71.

<sup>11</sup> Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasation, Final Report. October 23, 2019.

Regulatory action requiring monitoring and review of extravasations is fundamentally different from the majority of NRC specified medical events that can be attributed to failures to properly identify the patient, to execute the treatment plan, or failure to implant sources in the correct location – all of which are readily preventable.

Monitoring the rate of extravasations is a medical issue that is overseen by the institution's quality management program. Additional regulatory action would only add regulatory burden without an improvement for patient radiological health and safety.

Designating extravasations as a Medical Event would call for a dose estimation, which is far from a trivial process. Use of simplified techniques<sup>12,13</sup> do not effectively account for removal of the pharmaceutical from the injection site and the time varying geometry of the source, though they can be modified to do so with additional data collection. Simplified techniques can lead to large over-estimates of dose and potentially the number of Medical Events. More accurate evaluations require specific imaging of the patient, including the possible use of SPECT/CT (wherein the CT will contribute additional exposure with arguably minimal to no benefit), or Planar imaging to assess basic clearance from the infiltration site. These assessments require multiple time points, use staff and camera time, and inconvenience the patient who may be unwilling to comply with the additional time commitments and imaging. In hospitalized patients, the additional transportation of patients to and from the imaging suite will require additional hospital resources and may include additional medical risk. In addition, planar imaging alone is not likely to provide useful information regarding the volume of the infiltrate – which itself is time varying as the pharmaceutical is absorbed and translocates. If the licensee is held to a traditional 0.5 Sv trigger for medical events, the choice will be between investing the resources to show that infiltration is below this level, or relying on simplified techniques that will likely lead to an inflated count of medical events.

**NRC question:** *Are there any benefits, not related to medical techniques, to monitoring and reporting certain extravasations as medical events? What would be the burden associated with monitoring for and reporting certain extravasations as medical events?*

While we do not believe it is appropriate to classify extravasations as medical events, some oversight and trending is appropriate to ensure patient safety. For an extravasated radiopharmaceutical, the Authorized User should promptly take the appropriate medical

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<sup>12</sup> Shapiro B. Dosimetric consequences of interstitial extravasation following IV administration of a Radiopharmaceutical. *Eur J Nucl Med* (1987) 12:522-523.

<sup>13</sup> Castronovo FP, McKusick KA, and Strauss HW. The infiltrated radiopharmaceutical injection: Dosimetric considerations. *Eur J Nucl Med* (1988) 14:93-97.

intervention and report the incident to the Radiation Safety Officer and, where applicable the Radiation Safety Committee, as well as to the appropriate patient safety organization.

**NRC question:** *If the NRC were to require that licensees report certain extravasations as medical events (recorded in NMED), what reporting criteria should be used to provide the NRC data that can be used to identify problems, monitor trends, and ensure that the licensee takes corrective action(s)?*

The focus for intervention and patient safety should be on the potential tissue reaction aspects of these incidents. In this context, more appropriate triggers for whether a medical event has occurred than the use of the 0.5 Sv limit should apply. For example, transient erythema from fluoroscopic x-rays is thought to have a relative threshold of 2 Gy (200 rad), with higher dose leading to increased injury. Perhaps NRC should consider how the Medical Community handles fluoroscopic skin injury<sup>14</sup> if reassessing reporting of extravasations.

**NRC question:** *If the NRC requires reporting of extravasations that meet medical event reporting criteria, should a distinction be made between reporting extravasations of diagnostic and therapeutic radiopharmaceuticals? If so, why? If not, why not?*

In reviewing how to approach radiopharmaceutical extravasations, the NRC should consider how medicine monitors extravasations of chemotherapy agents. The response to these events focuses on identification and mitigation of physical injury through a variety of methods.

The NRC should consider the recommendations of ACMUI and not include diagnostic radiopharmaceuticals in any Medical Event program<sup>15</sup>. In its 2020 Report, ACMUI wrote that diagnostic administrations should not be considered Medical Events as “None of the total doses in these extravasations meet the NRC’s medical event criteria of a discrepancy of a total dosage of  $\pm 20\%$  delivered dose criteria.”<sup>16</sup>

Should NRC decide to classify extravasation as a Medical Event, we urge the NRC to focus on therapy administrations where there is a potential for patient harm in the form of tissue reactions. The NRC should consider in its analysis whether dose reconstruction adds value to the medical management of the injury. In its assessment, NRC should also consider that

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<sup>14</sup> The Joint Commission. Sentinel Event Alert 47: Radiation risks of diagnostic imaging and fluoroscopy. August 24, 2011. Revised February 2019.

<sup>15</sup> Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasation, Final Report. April 6, 2020.

<sup>16</sup> Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasation, Final Report. October 23, 2019.

infiltration and extravasation are events that are expected to occur at some frequency in medical practice regardless of interventions and quality initiatives.

## Response to the HPS Public Comments to Docket ID NRC-2020-0141

Dear Editors:

FOR 41 y, the US Nuclear Regulatory Commission (NRC) has cited a 1980 policy to exempt licensees from reporting extravasations that meet medical event criteria. After reviewing why attempts in 2008 and 2019 failed to remove an obviously incorrect policy, Lucerno Dynamics officially petitioned the NRC in May 2020 to remove the reporting exemption. The petition request specifically included a public comment period to encourage documentation of stakeholders' positions and to increase transparency in the decision-making process. Hundreds of comments were submitted, including one from the Health Physics Society (HPS).

We appreciate *Health Physics* providing an opportunity to examine the HPS public comment. To understand the appropriateness of the HPS comment, it is important to consider contextual information about the NRC, the petition, and HPS guiding values.

### NRC BACKGROUND

After incidents involving 426 patients at Riverside Hospital in Columbus, OH, from 1974–1976, the U.S. Congress cited a 1972 US Government Accountability Office report and directed the NRC to take an active role in protecting patients from accidental radiation exposures. An investigation into the Riverside overexposures concluded that a combination of human error, lack of training, and insufficient quality assurance processes contributed to injuring patients. In 1979, the NRC issued their first Medical Use Policy Statement, which was then modified in 2000:

1. US NRC will continue to regulate the use of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public.
2. US NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public.
3. US NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to

assure the use of radionuclides is in accordance with the physician's directions.

4. US NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

The NRC elaborated on Point 3 above regarding regulation of the delivery of radioactive material: "The Commission has a role in assuring accurate delivery of radiation doses and dosages to patients and has rejected the notion that NRC should not regulate patient radiation safety (44 FR:8243, February 9, 1979). NRC will continue to regulate the radiation safety of patients when justified by the risk to patients, primarily to ensure that the authorized user physician's directions are followed. The Commission recognizes that physicians have the primary responsibility for the protection of their patients. However, the NRC's role is also necessary to ensure radiation safety of patients."

In 1980, the NRC released misadministration reporting regulations *to ensure information was shared, radiation safety improved, and patients protected from inadvertent exposures/irradiation*.

In 2001, the NRC, taking a more "risk-informed" approach, raised the reporting threshold to 0.5 Sv and changed the term "misadministration" to "medical event." The NRC has consistently stated that exceeding misadministrations/medical event reporting criterion indicates that providers may have issues handling radioactive material. It does not necessarily suggest injury. *Patient harm is not a reporting criterion*.

Radiopharmaceutical administrations can be affected by human error, training levels, and quality assurance processes. Despite this, the NRC specifically excluded **all** extravasations from reporting, no matter the resulting dose to the patient tissue and skin. In the 14 May 1980 Federal Register, the US NRC exempted extravasations from reporting citing its understanding that extravasations were a frequent occurrence in intravenous injections and were "virtually impossible to avoid." The NRC logically concluded that if extravasations could not be avoided, there was no reason to report an event. As a result of the exemption and for the past 41 y, licensees have not been required to characterize and document extravasations nor to inform patients they have been extravasated, no matter the localized dose.

The NRC exemption was reconsidered in 2008–2009 by the Advisory Committee on the Medical Uses of Isotopes (ACMUI), and the ACMUI recommended retaining

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the exemption. A review of meeting transcripts reveals that ACMUI members knew that extravasations occur frequently in nuclear medicine, that training and experience are contributing factors, and that with proper attention they can be avoided. However, members were more interested in avoiding reporting rather than protecting patients. In discussing an extravasation where a patient received a dose equivalent to 6 to 10 times the reporting threshold, one member stated: *“Now if we consider this as a medical event, if we go through all the procedures and identify whatever—3 or 4 or 5 [sieverts]—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.”*

The US NRC reporting exemption is inconsistent with International Atomic Energy Agency (IAEA) guidance. On 17 August 2021, as part of a denial of three petitions, the NRC stated that the IAEA is an “international authoritative scientific advisory body” and that it “has been the longstanding practice of the US NRC to generally place significant weight on the recommendations” of such a body. Just months earlier, the IAEA published *QUANUM 3.0: An Updated Tool for Nuclear Medicine Audits*, which states that extravasations are not caused by patients but are preventable errors in the radiopharmaceutical administration process that should be documented and analyzed for root causes. Furthermore, the 2018 IAEA Technical Meeting, “Preventing Unintended and Accidental Exposures in Nuclear Medicine,” suggested in vivo imaging or radiation monitoring can play an important role after administration to confirm bio-distribution and/or exclude extravasation. IAEA also recommended stopping extravasations immediately and starting mitigation, assessing the local dose to tissue, monitoring patients, and informing the treating physician.

The NRC exemption also results in irrational and inconsistent reporting. In November 2019, a patient at Vanderbilt University Medical Center experienced an external leak of Lutathera. The localized dose was estimated to be 7 Sv. The patient experienced skin and tissue injury. *This event was reportable to the state of Tennessee and to the NRC. However, an extravasation of up to 207 mCi of Lutathera at a different center that same month was not reportable.* The exemption makes no logical sense. As radiotherapeutics grow in volume, centers that routinely extravasate diagnostic radiopharmaceuticals will start to administer therapeutics. Maintaining the 1980 policy will ensure significant diagnostic and therapeutic extravasations that meet reporting criteria will remain unreported.

## PETITION BACKGROUND

Lucerno stumbled onto the problem of extravasations. In 2014, we began a clinical study to assess radiopharmaceutical

uptake in breast cancer, but four of the first 15 study patients were extravasated. Two of the four extravasations were moderate-to-severe based on Quantitative Imaging Biomarker Alliance classifications and prevented use of the study data. In response, we validated our technology for monitoring excess radiotracer at the injection site through clinical studies at St. Louis University, and we also researched extravasations and their incidence rate. We learned that extravasations, while nearly eliminated in chemotherapy and contrast CT injections (0.18% and 0.24%, respectively), were significantly higher in nuclear medicine centers. Based on published studies of retrospectively reviewed images, extravasation rates averaged 15%.

To confirm the limited published studies, Lucerno sponsored the largest ever quality improvement (QI) project for radiopharmaceutical administrations. Seven centers, 56 technologists, and 5,551 patients participated. Even though technologists knew administrations were being monitored, center extravasation rates ranged from 2–16% during the QI project’s Measure Phase. Technologist rates ranged from 0–24%. When four centers used standard quality improvement methods, they cut their rates in half within two months ( $p < 0.0001$ ).

From conversations with vascular access experts, we confirmed that radiopharmaceutical extravasation rates were higher than necessary. Providers call these experts when they fail to gain venous access after multiple “sticks.” Using the latest technology and training, these venous access clinicians average 98% first stick success in arguably the most difficult patient population. The remaining 2% require additional access attempts; extravasation rates in this limited number of patients are well below 1%.

A review of chemotherapy and contrast CT extravasation rates, findings from the nuclear medicine QI project, and vascular access expert experiences all suggested that the premise for the NRC exemption was incorrect. Extravasations are NOT virtually impossible to avoid. Rather, radiopharmaceutical extravasations result from a lack of training, improper tools and techniques, and inadequate quality assurance processes. There is no rational reason to exclude extravasations from reporting if the resulting localized dose exceeds the existing reporting thresholds.

Clearly, the benefits of a nuclear medicine procedure easily outweigh the associated radiation risks when radiopharmaceuticals are properly administered. But a significant extravasation can change the benefit/risk relationship. Members of the nuclear medicine community have suggested extravasated diagnostic radiopharmaceuticals posed no patient safety concerns. This is false. After consulting with the world’s leading internal radiation dosimetry experts and learning how to perform dosimetry on extravasated patients, we discovered that diagnostic radiopharmaceuticals could result in very high tissue absorbed doses when extravasated. But there is a lack of awareness within the community.

Numerous nuclear medicine practitioners told us that  $^{99m}\text{Tc}$  is a “pure” gamma emitter, and they were unaware of  $^{99m}\text{Tc}$  electron and x-ray emissions as well as the localized dose they can contribute. For example, a 20 mCi  $^{99m}\text{Tc}$  extravasation can result in 5 Gy to 5 cm<sup>3</sup> of tissue. Similarly, 10 mCi of F-18 can result in 7.9 Gy to 5 cm<sup>3</sup> of tissue. The volume of 5 cm<sup>3</sup> of tissue is not insignificant.

While many extravasations may only represent a few microcuries left at the injection site, the significant extravasations described above are not rare. Our experience with over 24,000 injections shows approximately 1 in 5 extravasations represent from 5% to nearly 100% of the injected activity. Depending on the initially injected activity and initial volume of tissue infiltrated, significant extravasations can result in high doses. Furthermore, it is important to understand the state of the extravasation during the uptake period and prior to imaging. Using only static images to assess activity will underestimate the true extent of the extravasation.

Because significant extravasations occur routinely, can result in localized tissues doses that exceed reporting thresholds, and are preventable, there is no reason to exempt these inadvertent irradiations from reporting. Additionally, widely held misconceptions about extravasations, rapidly increasing use of radiotherapeutics, reluctance of the nuclear medicine community to inform patients, and an unwillingness of the community to invest in venous access training, tools, and techniques are reasons why approving the petition is necessary to ensure radiation protection of patients.

### HPS TENETS

HPS appears ideally positioned to provide extravasation guidance to the NRC, clinicians, and patients. The HPS website explains that it is a professional organization whose mission is to promote excellence in the science and practice of radiation safety. The website outlines an interest in ensuring HPS is a trusted source of radiation safety expertise and information for the government and public that enables the safe use of radiation to improve people’s lives. Furthermore, HPS advocates for radiation safety and scientifically sound information. Additionally, HPS has a Code of Ethics that lists principles by which members should determine the propriety of their conduct in relationships with governmental agencies and the public. Two principles of note include: “members shall never compromise public welfare and safety in favor of an employer’s interest” and “professional statements made by members shall have a sound scientific basis.”

In the public comment that was submitted to the NRC last year, HPS failed to live up to its principles and poorly represented the profession of radiation protection.

### HPS PUBLIC COMMENT ASSESSMENT

The HPS public comment to the NRC is inaccurate, misleading, inconsistent with international guidance and US regulations, and not supportive of the professional practice of radiation safety. The comment also violates the HPS Code of Ethics, in that it is a professional statement but does not have a sound scientific basis. One might also argue that the comment represents the positions of healthcare employers not interested in reporting significant extravasations rather than focusing on public welfare. While a complete detailed rebuttal with references was provided to the NRC last year, below are a few examples of how the HPS public comment fails to meet the Society’s own standards.

The HPS public comment leads with, “Labeling an infiltration as a Medical Event carries a fairly serious stigma, and yet there is no evidence that infiltration of radiopharmaceuticals carries any health consequences for the patient or the general public.” There is no scientific evidence to support this statement, but there is evidence that inadvertent ionizing radiation to healthy patient tissue can have health consequences for patients. Furthermore, the statement ignores the petition’s citation of over 60 peer-reviewed articles specifically demonstrating either known or potential health consequences to patients and ignores the database search results of adverse events related to extravasated radiopharmaceuticals. HPS then contradicts its own assertion by citing an article that specifically describes patient harm from a radiopharmaceutical extravasation. HPS contradicts itself again with the following statement: “We also acknowledge the specific concerns associated with the infusion of therapeutic agents and that extravasation of a therapeutic dosage of a radiopharmaceutical can result in potentially injurious radiation exposure to localized tissue.”

The HPS public comment provides yet another contradiction of patient consequences (side effects of therapeutic extravasations), as well as another reason to be disappointed. HPS states, “In nuclear medicine, however, there appear to be relatively few reports of side effects from extravasation of radiotherapeutic agents and no reports of side effects related to extravasation of diagnostic agents (with regard to localized radiation dose).” This diagnostic extravasation side effects statement is false. In fact, HPS cited a van der Pol et al. article that reports adverse tissue reactions from diagnostic radiopharmaceuticals. The authors state that of the 3,016 diagnostic radiopharmaceutical extravasations reported in the literature, only three had dosimetry performed and patients followed. All three suffered adverse tissue reactions. These reactions took 20 d, 2 y, and 3 y to manifest. In the remaining 3,013 diagnostic extravasations, dosimetry was not performed, and patients were not followed. Following these patients would have likely resulted in other examples of latent effects of radiation. Furthermore, if HPS searched adverse events or vigilance reports databases for

diagnostic radiopharmaceutical extravasations, it would have found further proof that its statement is incorrect.

The HPS public comment also includes sensational statements that can scare the public about additional radiation exposure and fixate providers on concerns of cost and time. HPS states, “If NRC considers extravasation a Medical Event, such a classification could force the estimation of the localized dose. Accurate measurement may require serial CT imaging of the site, which may result in additional patient dose simply for the purpose of complying with a regulation. This additional imaging would add substantially to the costs of doing any procedure, including facility, technologist, and physician time.” The HPS statement ignores current medical guidance, which states that if extravasation is suspected, clinicians should image the injection site to characterize activity. A regulation that calls for characterizing extravasations will not add additional radiation exposure to patients, beyond what clinicians should already do. Statements about cost and time are made without supporting data. Licensees are obligated to protect their patients from inadvertent radiation exposure. Just as licensees invest in quality control and assurance checks today to provide safe and effective studies, they should invest in the tools and training to ensure proper radiopharmaceutical administration. HPS suggests the NRC allow licensees to solve their extravasation problems without regulation, which shows their comments about time and cost are disingenuous. Licensees need to invest in training and tools to fix their problem, whether regulated or not. Centers are more likely to secure the necessary funds and time if regulations exist.

The HPS public comment also misrepresents several references. HPS states that “Extravasation is estimated to occur in 0.6% to 6% of radiopharmaceutical administrations.” HPS cites two references to support this statement, but neither is relevant. The first reference focuses on radiopharmaceutical extravasation consequences; it does not provide an extravasation rate. The second reference reviews chemotherapy extravasation rates, not radiopharmaceutical rates, from four studies conducted from 1980–1989.

An even more egregious example of misrepresenting references is the HPS statement that “Extravasations in nuclear medicine administrations are low in comparison to chemotherapy administrations, where the extravasation rate may be as high as 35 to 50%.” Here, HPS incorrectly cites a Nickel et al. article, which in turn references a 35–50% extravasation rate

from a Helm et al. article. This 35–50% rate is supported by four references, none of which discusses chemotherapy extravasation rates. All four references refer to hospitalized patients requiring long-term placement of IVs. It is irresponsible and lazy for HPS to misrepresent references like this to make a desired point.

The HPS comment also completely misrepresents the difficulty of the process to estimate dose to infiltrated tissue. It would seem the Society exaggerates dosimetry to discourage characterization of extravasations. In January 2021, *Health Physics* published a paper that describes a dosimetry method that is fast (3–5 min) and uses free software.

## SUMMARY

The NRC plays an important role in protecting patients from inadvertent exposure to radiation. Medical event reporting is designed to ensure preventable exposures are identified, lessons are learned, and information is shared to minimize unnecessary exposure to future patients. The current extravasation reporting exemption is based on an incorrect premise, and results in inadequate radiation protection during radiopharmaceutical administrations. The NRC is currently considering a petition that provides dispositive evidence that extravasations are *not* virtually impossible to avoid and that significant extravasations can easily exceed medical event reporting thresholds. The petition calls on the NRC to eliminate the 1980 extravasation reporting loophole. HPS opposed the petition with a public comment that is not based on sound science and violates their own Code of Ethics. To salvage its scientific reputation, HPS should withdraw their submitted comment and instead endorse the petition based on the science and evidence. By admitting its mistake and implementing a process to vet future public statements, HPS will demonstrate scientific integrity and start the process of rebuilding its reputation as a trusted source of radiation protection information.

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**Patients for Safer Nuclear Medicine (PSNM)  
Supports the Development of Federal Policies  
that Support Safe, Transparent, and Effective  
Nuclear Medicine Care on Behalf of Patients  
Throughout the U.S.**

*Dear Editors:*

Patients for Safer Nuclear Medicine (PSNM) is a national coalition of 27 patient and corporate organizations. Together, we are dedicated to the development of federal policies that support safe, transparent, and effective nuclear medicine care on behalf of patients throughout the U.S.

We are glad to see the Health Physics Society (HPS) fostering a discussion in the journal, *Health Physics*, about extravasation. This is an issue we feel deserves a fair and thorough public airing. We appreciate the opportunity for patients to raise their concerns about the public comments HPS submitted to the US Nuclear Regulatory Commission (NRC) in 2020 regarding petition PRM-35-22. In anticipation of the *Health Physics* extravasation edition, PSNM began preparing a comment. In addition, several of our members expressed their desire to represent the various patient perspectives on extravasations and also prepared their own submission.

However, to accommodate a last-minute request from HPS, PSNM has edited our comment to allow for inclusion from individual members. The comments below represent just a sample of the patient advocacy perspectives.

**TEEN CANCER AMERICA—SIMON DAVIES**

At the outset, it is important to stress that our concerns are not intended as a criticism of nuclear medicine, which is a vital contributor to the diagnosis and treatment of cancer. However, extravasation is a separate, serious matter—albeit one with a surprisingly simple solution.

With that said, the official HPS position expressed in a letter submitted to the NRC on 14 October 2020 raises several points to which we strenuously object.

The letter asserts, "...there is no evidence that infiltration of radiopharmaceuticals carries any health consequences for the patient or the general public." However, later in the same document, the HPS states, "We also acknowledge the specific

concerns associated with the infusion of therapeutic agents and that extravasation of a therapeutic dosage of a radiopharmaceutical can result in potentially injurious radiation exposure to localized tissue."

Beyond the self-evident contradiction in the acknowledgement that therapeutic extravasation can indeed harm the patient, there is clear evidence that significant diagnostic extravasations can also lead to high absorbed doses and adverse tissue effects. Simple logic dictates that ionizing radiation affects healthy tissue, and it is surprising that this is even a point of debate. There is zero patient benefit—and considerable potential downsides—when extravasation occurs. This is particularly troubling for the young patients we serve who are already living and coping with a cancer diagnosis. They have a long life to live and shouldn't be exposed to potential complications down the road from an extravasation.

There is another serious concern related to extravasation: stunningly, the patient may never even know that extravasation has occurred. This is because there is no patient notification requirement in the US. Since 1980, nuclear medicine providers have been required to report any unintentional, significant radiation exposure to the NRC. However, extravasations are excluded.

By removing the extravasation reporting exemption, the NRC will encourage nuclear medicine providers to recognize the value of developing quality control measures with a goal of preventing extravasations in the first place. Shining a light on extravasations will also provide the NRC with real-world data, not just anecdotes, to help identify underlying causes.

Simply put, failing to report significant extravasations also fails patients. In its position letter to the NRC, HPS argues that "Adding NRC oversight of extravasations will increase the regulatory burden without a radiological or patient safety benefit." We disagree in the strongest possible terms. We have yet to see a compelling argument in support of the status quo.

We take HPS at its word when it claims to promote excellence in the science and practice of radiation safety. We are baffled by the deeply flawed opposition to extravasation reporting. While resistance to increased regulation appears to be a driving factor, we hope that a thorough review of this issue will encourage opponents to consider the highest priority: the patient, who has every right to know when a radioactive drug has been improperly injected into their own body.

Young people living with cancer need to have faith in their providers. After all, they are literally putting their lives in the hands of medical professionals. We can help these patients—and many, many others—by closing the

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extravasation loophole. The NRC can provide patients with a level of transparency that leads to trust—and potentially better outcomes—by taking action that is decades overdue.

### **CACTUS CANCER SOCIETY—MALLORY CASPERSON**

The Cactus Cancer Society speaks on behalf of young adult cancer patients, survivors, and caregivers. Some members of our team are also cancer survivors. I am among them.

It is not an exaggeration to say that the current policy governing radiopharmaceutical extravasations in the US fails at the most basic level by utterly disregarding the patient. The opposition from the Health Physics Society to revising this policy is even more baffling and disappointing.

The official position of HPS, as outlined in an October 2020 letter to the NRC, contends that “Labeling an infiltration as a Medical Event carries a fairly serious stigma, and yet there is no evidence that infiltration of radiopharmaceuticals carries any health consequences for the patient or the general public.”

In its comments, HPS also claims that “Documentation of the survey and measurement of infiltration would need to be included in the medical record, adding further to additional burden and raising the issue of needlessly alarming patients.”

To which I can only respond: yes! Medical errors should be documented. Patients need to know. We are responsible for our health. And don’t worry about ‘needlessly alarming’ patients. This is a patronizing position. Respect us. Provide us with the information we need to know about what is happening with our own bodies.

I have read comments from several other medical societies. Many of them state that extravasations happen frequently. That is amazing, but even more amazing is that we lack the information to fully analyze the scope of the problem. A reporting requirement would undoubtedly encourage providers to take the issue of extravasation seriously, ensuring tracking and development of appropriate mitigation plans. In addition, reporting helps let patients know which nuclear medicine centers have the best records in administering medical isotopes.

We ask the HPS to revise their comments to the NRC. Use your voice to speak up and change the policy regarding extravasations. Please help improve cancer care for all.

### **YOUNG SURVIVAL COALITION—MARY FARRELL AJANGO**

On behalf of the Young Survival Coalition—a New York-based international organization focused on women 40 and younger who are diagnosed with breast cancer—we believe the current extravasation policy in the US does a grave disservice

to the patients we serve, and we have concerns with the Health Physics Society’s position on this issue.

It is said that knowledge is power. Patients who are armed with all information related to their condition are better able to advocate on their own behalf. We believe, without question, that patients have a right to know what is going on within their own bodies. Unfortunately, the current NRC policy on extravasations is diametrically opposed to this patient-centric view, and the HPS inexplicably agrees.

HPS weighed in on this issue in October 2020 with comments submitted to the NRC. While we take exception with HPS’s opposition in general, one assertion is particularly troubling: “The [ACMUI] report acknowledges that extravasation[s] frequently occur in normal intravenous procedures and are almost impossible to prevent. Such events are inconsistent with the stated purpose of a Medical Event.”

First, to be clear: extravasation should not be diminished by suggesting in any way that it is a “normal” part of the process. Furthermore, extravasations are not “almost impossible to prevent.” It is reasonable to expect that providers have procedures in place to not only reduce the potential for extravasation, but also to respond in a timely manner when a patient has been extravasated. There have been reports of providers drastically reducing the number of extravasations occurring at their facilities, which indicates that shedding light on the matter and developing effective internal policies can have a positive impact.

Ultimately, radioactive isotopes injected into tissue thwarts the intended purpose of the medical procedure and can result in compromised diagnostic images that have negative downstream effects on the patient’s treatment plan, as well as harmful biological effects to the patient. This is particularly true for young women with cancer, who have lives to live following treatment and do not need an extravasation causing additional future health concerns. These unintended consequences are quite consistent with the NRC’s stated purpose of medical event reporting.

HPS also states the following: “As stated by NRC’s Advisory Committee on the Medical Use of Isotopes (ACMUI), ‘The prevention of extravasation is a medical training issue for the authorized user (AU) physician and the technologist under the supervision of the AU, which is considered medical practice and not something that needs NRC regulation.’”

This assertion simply doesn’t add up. The NRC’s federally authorized role is to ensure the correct administration of radiopharmaceuticals to protect patients from misadministration and potential for physical harm. Under that definition, the role of the NRC extends to potentially harmful extravasations, which are literally misadministration of nuclear material.

Now is the time to speak up and take a stand to protect the patients we collectively serve. They are vulnerable

and need to see that as medical professionals, as advocates, and as fellow human beings, we will contribute to an improved process of cancer diagnosis that, in turn, can contribute to better outcomes.

### ICAN, INTERNATIONAL CANCER ADVOCACY NETWORK—MARCIA HORN

The debate around radiopharmaceutical extravasation reporting is reaching a fever pitch. As President and CEO of ICAN, the International Cancer Advocacy Network, a national patient advocacy and research organization, I appreciate the attention being paid to this vital patient care issue by the Health Physics Society (HPS) and thank HPS for this opportunity to speak up.

Unfortunately, the official position of HPS is on the wrong side of this debate. I, for one, hope they will reconsider requiring significant extravasation reporting and look at the matter through a patient's eyes.

Arguments against radiopharmaceutical extravasation reporting frequently center on the assertion that there is no need for reporting because facilities already monitor for such events. In comments supporting the status quo, provided to the US Nuclear Regulatory Commission in October 2020, HPS makes the argument that "Nuclear medicine clinics currently monitor for radiopharmaceutical extravasation."

This assertion is highly questionable at best because there is no data in support. If no one is required to report extravasation, how could this be known? Even a recent survey of eight top cancer centers conducted by Vascular Wellness found that not a single facility had protocols in effect for significant extravasation. This matter is far too potentially harmful to patients to leave up to a quasi-honor system that few appear to actually be honoring.

And make no mistake: there is a big problem. It is not disputed that extravasation occurs. We have plenty of anecdotal evidence. For example, during a recent virtual event on the issue, I heard from a patient who was extravasated at one of the best-known and highly respected healthcare institutions in the US. The technologist had no idea extravasation had occurred; even worse, the technologist had no idea what to do after the patient made the technologist image the injection site and identify the extravasation.

If the approximately 7,500 nuclear medicine clinics in the US were actively monitoring for extravasation, then it is reasonable to expect that estimated rates would be far lower.

Regulatory oversight would drive improvements that benefit patients. Yet HPS, in its comments on the issue, disagrees: "Monitoring the rate of extravasations is a medical issue that is overseen by the institution's quality management program. Additional regulatory action would only add regulatory burden without an improvement for patient radiological health and safety."

The HPS position that radiation safety represents a "regulatory burden without an improvement for patient radiological health and safety" irresponsibly waves away the very real adverse consequences of serious extravasation events.

Extravasation has very real, downstream effects: the patient may come to severe physical harm around the injection site, which can take months or even years to manifest. In addition, the images may be compromised, which can result in misdiagnosis and a flawed treatment plan.

Furthermore, we know from speaking with extravasated patients who were not notified—and suffered visible, obvious complications as a result—that their imaging procedures were not repeated. There are currently no standards in place that require a repeated imaging study in the event of extravasation.

Patients' lives are in the balance. Time is of the essence. Please consider the responsible approach of urging the NRC to require extravasation reporting. It is the only policy that correctly places the patient at the center of all that we do.

### UPPI LLC—JOHN WITKOWSKI

Established in 1998, UPPI is a leader in traditional nuclear medicine and the growing nuclear and PET pharmacy industries. We represent more than 80 independent and institutional operating sites across the country. We are a proud member of the Patients for Safer Nuclear Medicine Coalition and stand by patients in their concern with the HPS comments to the US Nuclear Regulatory Commission (NRC).

Imaging and radioactive therapy have been part of medicine for more than five decades. Looking into the future, new radiopharmaceuticals for imaging and therapy, known as radiotheranostics, are in stages of development and will eventually be approved for human use.

These products will expand the use of alpha and beta emitting drugs, leading to the development of nanoparticles and expansion of other forms like radiolabeled microspheres. In advance of these innovative products, the NRC created a subpart in its regulations for licensing new and emerging radiopharmaceuticals [see Title 10 of the *Code of Federal Regulations* Part 35, Subpart K—Other Medical Uses of Byproduct Material or Radiation From Byproduct Material (10 CFR 35.1000)].

This growth in radiopharmaceutical development to precisely image and treat tumors and metastatic spread will include the major cancer populations—prostate, breast, colon, and lung. Nuclear medicine with theranostics will provide an armamentarium of radioactive drugs prognostically beneficial to patient survival. That means more candidates will be eligible for care with radiopharmaceuticals administered through injections.

To that end, it is essential to have the medical community actively involved in educating patients about

radiopharmaceutical injections by monitoring and providing follow up care to help prevent the unintended consequence of extravasations. The health physicist will become part of the patient care team and see its expertise expand to encompass new and emerging radiopharmaceuticals involving alpha and beta emissions.

A recent article in *Endpoints* stated that Xofigo® (Radium-223 first-in-class alpha emitting therapy in prostate cancer) was administered in 80,000 patients worldwide since its approval. A full course of Xofigo therapy is six injections over a time span based on patient response. More than 80,000 injections were prescribed and administered, and the probability of extravasation is present. The NRC has exempted extravasations as a Medical Event for over 40 years. The rapid expansion of nuclear imaging and radiotherapies requires a change in policy. Medicine has a passion for patient care, and passion is needed for the nuclear medicine patient involving extravasations of radiopharmaceuticals.

#### **PATIENTS FOR SAFER NUCLEAR MEDICINE**

PSNM also includes corporate partners interested in improving radiopharmaceutical administration quality and patient safety in nuclear medicine. They represent radio pharmacies, vascular access professionals, and healthcare education resources. On their behalf, PSNM adds the following points to those made by our individual patient advocacy members.

The HPS public comment does not acknowledge that diagnostic extravasations can result in high, potentially harmful doses to patient tissue. We have seen with our own eyes in PSNM meetings that patients have experienced harmful diagnostic extravasations. Furthermore, Petition PRM-35-22 notes that extravasations can exceed the threshold that triggers medical event criteria, but they are not reported because of an exemption created by an outdated, unjustifiable 41-year-old US NRC policy. Even the Advisory Committee on

the Medical Uses of Isotopes (ACMUI), which has advised for 40 y to retain the reporting exemption, recently acknowledged that diagnostic extravasations can exceed the NRC medical event reporting criterion and can harm patients. The HPS position on this point is not correct.

PSNM recognizes that HPS is uniquely positioned to provide the NRC with radiation protection guidance. In this role, HPS guidance also influences other societies and individual clinicians. After reviewing numerous public comments and even the NRC Medical Staff's recent findings from their independent evaluation, it is obvious to us that many of the HPS statements from their public comment are being mimicked by others. This is concerning to us. Even though we are not radiation protection experts, it is clear to us that the HPS public comment is not correct. As we have shared with Dr. Cardarelli, the president of HPS, we believe the statement from HPS does not reflect "excellence in the science and practice of radiation safety."

With these points in mind, we call on the HPS to amend its public comment to the NRC. Furthermore, we call on the HPS to notify medical societies, such as ACR and SNMMI, once the amendment has been issued.

We strongly encourage you to focus on the patients and not on the politics of medical societies. Nothing good ever comes from an extravasation of a radiopharmaceutical. We agree with the ACMUI patient advocate, Ms. Laura Weil, when she stated that significant extravasations should be reported to the NRC no differently than any other medical event. It is time for HPS to agree.

MARCIA HORN

*ICAN Phoenix, AZ*



## A Request for Scientific Accountability in Public Statements

Dear Editors:

Scientific members of the health physics community come from many geographical as well as disciplinary areas. What they all share, though, is a commitment to excellence in the science and practice of radiation safety. It is through the lens of this commitment that we have tried to reconcile recent public statements concerning the topic of radiopharmaceutical extravasations—including those made by the Health Physics Society (HPS).<sup>1</sup> We acknowledge that the topic of extravasations is generating passionate discussions within the community, but HPS public comments should remain grounded in scientific truth; those that are not based on sound science should be withdrawn to preserve trust and further the highest standards of integrity.

First, published scientific literature does not support the assertion that “...there is no evidence that infiltration of radiopharmaceuticals carries any health consequences for the patient or the general public.” In fact, numerous publications (Breen and Dreidger 1991; Williams et al. 2006; Siebeneck 2008; Bonta et al. 2011; Terwinghe et al. 2012; Kawabe et al. 2013; Benjegerdes et al. 2017; van der Pol et al. 2017; Willson 2019) report the opposite—that accidental paravenous injection of radiopharmaceuticals can and has led to radiation-induced harm. It is important to recognize, though, that injury may not manifest for weeks or years (van der Pol et al. 2017)—possibly leading to an underappreciation of extravasation occurrence and significance.

Second, the HPS position that “Accurate measurement may require serial CT imaging of the site, which may result in additional patient dose simply for the purpose of complying with a regulation” is misleading. As pointed out by Fass et al., “CT imaging cannot characterize, and therefore is not used to characterize, the radioactivity of a radiopharmaceutical extravasation. Characterizing an extravasation does not

require any additional patient radiation dose. This HPS position statement is clinically incorrect and misrepresents the characterization process by implying it will result in increased patient radiation dose from serial CT imaging.”<sup>2</sup> Any good radiation safety program would expect unintentional exposures to be followed by accurate estimation of dose; however, CT imaging would not be at all necessary. CT would not provide an accurate measure of the size or distribution of an extravasation and is not even capable of determining severity, which must be based on radioactive concentration. Other methods, though, including but certainly not limited to emissive imaging, could be used with no additional radiation to the patient.

Similarly, the comment that “...Designating extravasations as a Medical Event would call for a dose estimation, which is far from a trivial process. Use of simplified techniques do not effectively account for removal of the pharmaceutical from the injection site and the time varying geometry of the source...” fails to consider the goals of such a dose estimation. As is routine in response to unintentional exposures, simplifications are acceptable with the goal being a reasonable estimate of dose within an overall radiation safety program. One would not excuse a radiopharmaceutical spill by explaining that the dosimetry is too hard. We, as health physics professionals, are able to make reasonable and educated estimates in these circumstances. In commenting on this topic, Dr. Fisher, a current member of the Society of Nuclear Medicine and Molecular Imaging Medical Internal Radiation Dosimetry Committee (SNMMI MIRD), past member of the Nuclear Regulatory Commission’s Advisory Committee on Medical Use of Isotopes (NRC ACMUI), and president emeritus of the HPS said, “...regardless of the serious nature of the dose, each extravasation to a patient’s arm should be monitored and characterized as a proper health physics practice. Better understanding of the frequency and character of extravasation events can lead to procedure review, continuous learning, and improvement in administration quality.”<sup>3</sup>

HPS goes on to say that “The response to these events focuses on identification and mitigation of physical injury...we urge the NRC to focus on therapy administrations where there is a potential for patient harm in the form of tissue reactions.” The implication that extravasation of radiopharmaceuticals intended for diagnostic use is de facto

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<sup>1</sup>[http://hps.org/govtrelations/documents/hps\\_nrc\\_extravasation\\_comments\\_10-14-2020.pdf](http://hps.org/govtrelations/documents/hps_nrc_extravasation_comments_10-14-2020.pdf).

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Dr. Kiser has provided consultancy services to Lucerno Dynamics in the past. Dr. Sullivan has provided manuscript editing services to Lucerno Dynamics in the past. All other authors declare no conflict of interest.

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<sup>2</sup><https://www.regulations.gov/comment/NRC-2020-0141-0488>.

<sup>3</sup><https://www.regulations.gov/comment/NRC-2020-0141-0362>.

unable to contribute appreciable tissue absorbed dose is without scientific basis. As experts in radiation physics, this community should be most capable of recognizing that absorbed energy is the quantity of interest here, no matter its origin. Locally absorbed positron energy from a significant  $^{18}\text{F}$  extravasation may be just as significant as that from a minor  $^{177}\text{Lu}$  extravasation (Tsorxe and Hayes 2021). It would be an irresponsible misapplication of scientific principle to propose that absorbed dose from diagnostic radiopharmaceuticals is inherently negligible in cases of extravasation. Rather, dosimetry should be performed to determine significance no matter the source.

Lastly, we would like to address the statement that "...infiltration and extravasation are events that are expected to occur at some frequency in medical practice regardless of interventions and quality initiatives." We of course acknowledge that unintentional exposures do happen under even the most stringent radiation protection programs. Inevitability of an occasional occurrence does not preclude the need for interventions and quality initiatives. Dr. Morgan, past Director of the HPS, clearly stated this when he said, "...reasonable efforts should be made to assess how and why extravasations occur so that appropriate measures can be taken to prevent reoccurrences...the major benefit would be collecting and analyzing data on how often these events occur and why" (Morgan 2020). We agree with the International Commission on Radiological Protection's (ICRP) position that extravasations should be characterized with dosimetry and records should be maintained. Quoting Dr. Fisher again, "Unfortunately, taking a polar opposite view, the Health Physics Society position statement embraced the idea that extravasations are not sufficiently serious considerations for patient radiation safety, that extravasation is a practice of medicine issue (not a regulatory responsibility), and that identifying, measuring, characterizing, and documenting this class of radiation accidents are unnecessary and burdensome activities for the clinic. The Society position statement directly contradicts standing NCRP and ICRP recommendations on these critical points."

As scientists and professionals, it is our duty to continually learn and improve. We challenge the HPS to lead from a position of scientific expertise and credibility, and we ask for an official renunciation and correction of previous statements made regarding extravasations. To quote the Health Physics Society's own Code of Ethics, "Professional statements made by members shall have sound scientific basis. Sensational and unwarranted statements of others concerning radiation and radiation protection shall be corrected, when practical."

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## Radiopharmaceutical Extravasation: Pragmatic Radiation Protection

Darrell R. Fisher<sup>1</sup> and Misty Liverett<sup>2</sup>

**Abstract**—Inadvertent injection of a radiopharmaceutical agent into a patient's arm tissue instead of into the appropriate blood vessel can cause the injection to infiltrate underlying tissue and produce a potentially substantial, localized irradiation to the patient's arm and skin tissue. When this type of misadministration occurs, called an extravasation, it should be recognized, mitigated, and monitored for patient health and safety. Immediate symptoms of radiopharmaceutical extravasation may include swelling, edema, pain, or numbness in the vicinity of the extravasation site; inflammation; and drainage from the site. Some infiltrations may go unnoticed until later. Pragmatic elements of radiation safety include imaging to assess the geometry, volume, and anatomic distribution of activity, collection of tissue count-rate data over retention times, calibration against known activity levels, and dosimetry to help clinicians determine whether an extravasation is severe and whether the patient should be followed for adverse tissue reactions.

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**Key words:** radiopharmaceutical extravasation; event characterization; dose assessment; radioactivity; radiation protection; external measurements

INADVERTENT INJECTION of a radiopharmaceutical agent into a patient's arm tissue instead of into the appropriate blood vessel can cause the injection to infiltrate underlying tissue and produce a potentially substantial, localized irradiation to the patient's arm and skin tissue. When this type of misadministration occurs, called an extravasation, it should be recognized, mitigated, and monitored for patient health and safety. Immediate symptoms of radiopharmaceutical extravasation may include swelling, edema, pain, or numbness in the vicinity of the extravasation site; inflammation; and drainage from the site. Some infiltrations may go unnoticed until later. Pragmatic elements of radiation safety include imaging to

assess the geometry, volume, and anatomic distribution of activity, collection of tissue count-rate data over retention times, calibration against known activity levels, and dosimetry to help clinicians determine whether an extravasation is severe and whether the patient should be followed for adverse tissue reactions.

Radiopharmaceuticals are usually administered intravenously. Extravasation refers to the unintentional or inadvertent injection of some of the radiopharmaceutical into surrounding arm tissue instead of directly into the vein (Hadaway 2007). Extravasations can also occur with (and protocols are established for) other injected substances, such as CT and MRI contrast agents. Injection into arm tissue instead of the intended vascular pathway and subsequent diffusion into surrounding tissue may also be referred to as an infiltration. Extravasated radiopharmaceuticals cause an unplanned, localized radiation dose to affected tissues. Consequently, radiopharmaceutical extravasations may result in mild to severe adverse tissue reactions.

Why does this happen? Sometimes the radiopharmaceutical is improperly administered to a patient. Injected solution escaping from its intended vein or artery diffuses into and accumulates in perivascular tissue (cells, intercellular material, interstitial fluid, and interstitial compartments). Unintended infusion may occur, for example, when the needle or cannula (1) causes a vein or artery to rupture, (2) improperly punctures the vein or artery, (3) backs out of the vein or artery, (4) leaks from improperly sized supplies, (5) administers infusion pump fluid at an excessive flow rate, or (6) increases permeability of the vein or artery.

### ADVERSE CONSEQUENCES OF EXTRAVASATIONS

The principal concern for extravasation of radiopharmaceuticals is radiation dose and tissue damage. Adverse biological effects reported in the literature include inflammation, localized pain (burning sensation), numbness, erythema, swelling (edema), lesions, wet and dry desquamation, severe tissue damage, and radiation necrosis in the vicinity of the extravasation site (van der Pol et al. 2017; Breen and Dreidger 1991; Terwinghe et al. 2012).

One case reported of local damage from a radium-223-dichloride therapy misadministration resulted in an

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aggressive squamous cell carcinoma at the injection site (Benjegerd et al. 2017). A further clinical concern is failure to deliver a prescribed amount of radiopharmaceutical to the intended target organ or tissue and consequently failure to image or treat the patient properly (Hall et al. 2006; Osman et al. 2011). Although extravasations for most diagnostic agents impart relatively small radiation doses, the increasing use of high-dose theranostic agents (for simultaneous diagnosis and therapy) requires a new look. With these new agents, additional care must be exercised to ensure that high-activity radiopharmaceuticals are completely delivered into the appropriate artery or vein.

### EVENT FREQUENCY

Most extravasations are not considered serious, but severe cases have been documented in journal articles. Published studies, anecdotal case reports, and personal experience show that inadvertent extravasations occur with surprising frequency and that the nuclear medicine technologists may not know what to do next (Osborne et al. 2021). Furthermore, health physics professionals may not be called upon to assist with characterization of severity, measurement data, and dosimetry; the medical clinic may not always recognize the need for post-incident characterization and medical follow-up. Relatively few extravasation events with adverse tissue reactions are reported in the medical literature.

Reviews of the frequency of extravasations show that these events occur about 10 to 15% of the time, on average, where the typical range is 1.3% to 28%. Osborne et al. (2021) reported that extravasations occur frequently (mean 10.4% of radiopharmaceutical infusions,  $n = 5,418$ , covering 20 nuclear medicine centers). Event frequency often depends on the training and experience of clinicians and technologists. With increasing use of high-dose therapeutic infusions, the number of serious events associated with radionuclide therapy has been increasing.

### PRAGMATIC RADIATION PROTECTION

To determine extravasation severity, each incident should be recognized, monitored, and mitigated as needed for patient health and safety. Health physicists and radiation safety officers can provide technical support to the nuclear medicine clinic. Essential measures include medical imaging to identify infiltrated tissue geometry and proximity to overlying skin, assessment of the activity biodistribution within and clearance from the infiltration area, collection of tissue count-rate data over relevant time periods, calibration against known activity levels, and radiation dosimetry for affected tissues.

Details should be documented in the patient medical record. Better understanding of the nature and frequency of inadvertent misadministrations can be helpful for procedure

review, continuous learning, and quality improvement in radiopharmaceutical delivery.

### RADIATION DOSIMETRY

The two tissues of concern for adverse reactions include (1) the infiltrated dermal and fascia tissues and (2) the proximate basal cell layer of skin epithelium (Osborne et al. 2021). Medical Internal Radiation Dose (MIRD) methods (Bolch et al. 2009) may be used to calculate the absorbed dose to infiltrated tissue and skin.

### REGULATORY DOSE LIMITS

National and international scientific advisory bodies provide recommendations and dose limits to extremities and skin for patient radiation safety to protect against inadvertent extravasation events. When diagnostic or therapeutic radiopharmaceuticals extravasate, the resulting doses may exceed established dose limits for skin and extremities (Osborne et al. 2021).

The National Council on Radiation Protection and Measurements (NCRP 2018) recommends calculating dose to both skin and extremities in gray (Gy), with a dose limit of 0.5 Gy. In the United States, federal regulations in 10CFR20 set forth dose limits for both extremities (affected arm and hand tissues) and for skin (at the sensitive basal cell layer for the highest relevant 10 cm<sup>2</sup> area).

### RECOMMENDATIONS FOR RADIATION PROTECTION

Acknowledging that extravasations can result in severe soft tissue lesion, the International Commission on Radiological Protection (ICRP) addressed the need to reduce or prevent medical errors involving misadministered radiopharmaceuticals. The ICRP recommended that patients should be monitored for extravasation during infusion, that the extravasation should be characterized with dosimetry, and that measurement results and dosimetry should be maintained in the patient medical record. ICRP Publication 140 (ICRP 2019, pp. 61–62) states:

*Intravenous infusion of therapeutic radiopharmaceuticals must take place via an appropriate venous access device to ensure safe administration and prevent extravasation. Patients should be monitored for extravasation during infusion. In the event of extravasation, the infusion must be halted immediately. Extravasation can result in severe soft tissue lesions. Although there is no specific treatment, local hyperthermia, elevation of the extremity, and gentle massage may promote spreading of the radiopharmaceutical and reduce the local absorbed dose. The event must be recorded, and follow-up is advised.*

Highlights from the ICRP Publication 140 recommendations include:

- extravasations by radiopharmaceuticals can cause severe soft-tissue lesions;
- extravasations should be characterized and followed for adverse reactions;
- patients should be monitored for extravasation during infusion of radionuclide therapy agents; and
- if an extravasation occurs, the infusion should be halted.

### SUMMARY

Since adverse biological effects correlate with the amount of radiation imparted, extravasation characterization by health physicists is essential and pragmatic for evaluating the radiation dose to patient arm tissue and overlying skin. Event characterization and dosimetry help physicians to determine whether an extravasation is severe and whether the patient should be followed and treated for adverse tissue reactions.

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