From:	RulemakingComments Resource
To:	RulemakingComments Resource
Subject:	FW: Petition for Rulemaking: Reporting Nuclear Medicine Injection Extravasations as Medical Events [Docket No. PRM-35-22; NRC-2020-0141]
Date:	Tuesday, March 16, 2021 3:45:38 PM
Attachments:	2021-03-15 NRC Public Comments Analysis_signed.pdf

From: Daniel Fass <drfass@medpark.us>
Sent: Tuesday, March 16, 2021 11:23 AM
To: Williams, Kevin <Kevin.Williams@nrc.gov>
Cc: Hanson, Christopher <Christopher.Hanson@nrc.gov>; david.crowley@dhhs.nc.gov; Ron Lattanze <rlattanze@lucernodynamics.com>
Subject: [External_Sender] Petition for Rulemaking: Reporting Nuclear Medicine Injection Extravasations as Medical Events [Docket No. PRM-35-22; NRC-2020-0141]

Dear Mr. Williams,

I am a radiation oncologist with over 35 years of clinical experience. I was the Chief Resident in Radiation Oncology at NYU Medical Center and went on to be the Brachytherapy Fellow at Memorial Sloan Cancer Center and served on the faculty for 6 years prior to opening my own practice. I was the principal investigator in the effort to incorporate Three-Dimensional Conformal Radiation Therapy into treatments for head and neck cancer. Now, I consult globally to develop cancer programs in emerging markets.

In late 2020, I was informed by a friend of recent developments regarding radiopharmaceutical extravasations. During my medical career, I have referred thousands of patients for nuclear medicine imaging procedures and have personal experience with the topic. As I researched the latest developments, I became aware of the petition before the Nuclear Regulatory Commission (NRC) and the submitted public comments. I was dismayed when I read comment 444 from The American Society for Radiation Oncology (ASTRO).

The comment states that “ASTRO’s highest priority has always been ensuring patients receive the safest, most effective treatments.” The rest of the ASTRO comment reveals that the authors do not understand extravasations nor the current exemption for reporting of extravasations. Furthermore, the comment is inconsistent with ensuring patients receive the safest, most effective treatments.

With the exception of the comment submitted by the Association for Vascular Access (which is supported by sound science), comments from other medical societies and their leaders are also dismaying. These comments reflect a stunning level of misunderstanding and downright misrepresentation by people who should know better.

To learn more, I reached out to the petitioner, Mr. Ron Lattanze, in February of this year. Prior to this call, I had no relationship with Mr. Lattanze or Lucerno Dynamics and to be transparent, I have no vested financial interest in this matter. Mr. Lattanze informed me that there were several experts who were just as concerned as I was with the lack of scientific understanding and misrepresentations by medical societies, their leadership, as well as members of the NRC’s Advisory Committee on the Medical Uses of Isotopes (ACMUI). When I became aware that this group of experts was reaching out to the NRC and Organization of Agreement States (OAS), I offered to help.

I have attached a document from these experts and me to this email. This document provides example comments that ignored scientific principles, made misrepresentations, or made incorrect statements or incorrect citations. Many of these comments were submitted by ACMUI members, medical societies, and their leaders. The document also provides factual corrections to these example comments; these factual corrections are supported with peer-reviewed references. The examples in the attached document reflect only a small sample of what we could have provided. Additionally, this document is timely. The American College of Radiology (ACR) recently sent a letter to Chairman Hanson. In their

correspondence, the ACR noted that “The President has promised a recommitment to science by executive departments and agencies. In that vein, we hope the NRC will appropriately elevate the expertise of medical licensees, physician specialists dealing with radioactive materials, medical physicists, and other experts on 10 CFR §35 issues.” In this letter to Chairman Hanson, the ACR proceeded to restate many of their same positions they submitted in their public comment last November. Ironically, these comments demonstrate that the ACR and others who espouse similar comments do not understand the science of extravasations. Many of the ACR statements are addressed in the attached document.

We hope you and your team find this information helpful as you consider the petition comments in the context of radiation safety and the protection of patients. We understand that many others are involved in the decision process and have copied the Chairman of the NRC, the Chairman of the OAS, as well as the petitioner.

Sincerely,

Daniel Fass, MD

Cc: Christopher Hanson, Chairman U.S. Nuclear Regulatory Commission
David Crowley, Chairman Organization of Agreement States
Ron Lattanze, CEO Lucerno Dynamics, LLC

March 15, 2021

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

Delivered via email

Dear Mr. Williams,

In May 2020, the NRC received a petition for rulemaking regarding (PRM-35-22). The petition provided evidence that a 1980 NRC policy that exempts all nuclear medicine extravasations from reporting *is inconsistent* with current medical event reporting requirements. We are scientists and clinicians who know this subject matter and have no vested interest in the outcome of the petition. Since this topic will be examined closely by radiation safety professionals, we thought that it would be important for the NRC to be aware of our findings.

We reviewed the public comments and found that many **simple science principles were ignored or described incorrectly**. Three areas of concern are summarized below and are supported with more detail in Appendix A.

Radiation emissions of diagnostic radiopharmaceuticals
Some of the public comments ignored the important contributions to extremity dose from short-range (nonpenetrating) ionizing emissions (beta+ and beta- electrons, internal conversion electrons, and Auger electrons) and low-energy photons and x-rays associated with diagnostic radiopharmaceuticals. Energy deposition from these emissions can result in relatively high, localized absorbed doses to extravasated tissues.

Extravasation causes, symptoms, and biological effects
Many public comments ignored the published scientific papers that describe the ways intravenous access and administration techniques can lead to extravasations, how the extravasated radiopharmaceuticals disperse and clear over time, how localized ionizing radiation injures tissue, and how latent radiation injury effects can take months or years to appear. We maintain that patients should be informed of events that could compromise their health.

Medical event regulations and the role of federal and state regulators
Some public comments ignored the responsibility that government has to regulate nuclear byproduct materials. Radiation dose limits have scientific underpinnings from national and international scientific advisory bodies. The practice of medicine argument ignores the potential significant radiation doses and harm to arm tissues from regulated byproduct materials. Radiopharmaceutical misadministrations should be monitored to characterize extravasation severity, severe cases should be mitigated, and patients followed for long-term consequences.

We also discovered **misrepresentations of facts, incorrect statements, and incorrect citations** during our analysis of submitted public comments. Other incorrect statements appear in the transcript of a meeting between the NRC Commissioners and members of the Advisory

Committee on the Medical Uses of Isotopes (ACMUI), and the transcript from the December 8, 2020 public comment WebEx. Several representative examples are provided in Appendix B.

We hope that you will seriously consider these errors of science and fact as you deliberate your next steps in the matter of radiopharmaceutical extravasations in medical patients.

Sincerely,

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APPENDIX A

Radiation emissions of diagnostic radiopharmaceuticals	
Representative statements (comment number)	Fact-based corrections
1. ACR 441: The petition and corresponding documentation cite literature related primarily to extravasations from non-radiological contrast media and cytotoxic chemotherapeutic instillations. These invariably consist of large volumes of substances with inherently tissue-damaging properties and are often administered with large-volume infusions over a long interval, often unattended. They are not analogous to administrations of radiopharmaceuticals, which are typically small volume, without inherent properties harmful to tissues	1. The American College of Radiology incorrectly described the relationship between the administered radiopharmaceutical volume and biological risk to tissue. It is clear that the amount of radioactivity, its biological clearance rate, and the volume of infiltrated tissue determine the absorbed dose, not the administered volume of radiopharmaceutical.(1, 2) The administered volume of radiopharmaceuticals can be extraordinarily small and still result in an absorbed dose that exceeds the reporting limit. A typical 18F-FDG administration of 10 mCi (370 MBq) may represent approximately 1 cc of administered volume. However, 0.067 cc (67 µL) representing 0.67 mCi of activity extravasated into 5 cc of tissue with a 30-minute effective half-life would result in an absorbed dose of 0.5 Gray. Additionally, the ACR ignored the damage from short-range (non-penetrating) and low-energy x-ray emissions from radioisotopes used routinely in diagnostic nuclear medicine (3).
2. Senior CNMT UC Davis – 110: gamma ray emitting radiotracer which has very negligible effects on the skin if infiltrated and is not at risk of being harmful	2. While gamma rays contribute to absorbed dose and biological tissue damage after an extravasation, the short-range (non-penetrating) and low-energy x-ray ionizing radiation emissions will contribute the most dose that damages tissue fascia and skin (3).
3. CNMT UC Davis – 131: diagnostic agents pose negligible threat to a patient's condition and injection area.	3. ***If properly administered***, diagnostic radiopharmaceuticals pose negligible threat to the patient and the injection site. However, that is not the case when the radioactivity is inadvertently concentrated at the injection site in the surrounding tissue outside of the intended vein (4).
4. CNMT in PET Ocala, FL – 23: There should be a clear distinction between diagnostic and therapeutic radiopharmaceuticals. Therapeutic radiopharmaceuticals are intended to damage and destroy tissue, similar to chemotherapy and other drugs.	4. Ionizing radiation from positron-emitting diagnostic radiopharmaceuticals (5) and ionizing radiation from internal conversion electrons, Auger electrons, and low-energy photons from diagnostic radiopharmaceuticals can damage tissue (1-3). In the administration of both diagnostic and therapeutic radiopharmaceuticals, an extravasation leads to unintended irradiation of normal (non-cancer) tissues.
5. Anonymous – 6: a distinction should be made between reporting extravasations of diagnostic and therapeutic radiopharmaceuticals, specifically those that pertain to therapeutic radiopharmaceuticals as most current diagnostic materials do not result in substantial harm to the patient.	5. See #4 above. Additionally, diagnostic radiopharmaceutical extravasations can result in high absorbed doses to the tissue (4) and therefore should be reportable when doses exceed the specified medical event reporting criteria.
6. CNMT Michigan – 27: the radiation dose from a diagnostic test is minimal, especially with the majority of the isotopes having relatively short half-lives.	6. The radiation dose from diagnostic tests is minimal if the radiopharmaceutical is administered completely into the venous system. However, if extravasated, these diagnostic radiopharmaceuticals can cause a very high absorbed dose to the effected localized tissue. Published literature shows that short-lived isotopes used in nuclear medicine can be harmful when injected into arm tissue (4).

Radiation emissions of diagnostic radiopharmaceuticals	
Representative statements (comment number)	Fact-based corrections
7. Leading members of SNMMI – 425: An extravasated radiopharmaceutical administration would never deliver 0.5 Sv (50 rem) to any whole organ or tissue, including the skin	7. Representatives of the Society of Nuclear Medicine (SNMMI) selectively ignored the 26 extravasation events that are identified and described in the journal Health Physics (4). The science clearly shows that extravasated radiopharmaceuticals can deliver doses greater than 0.5 Gy or 0.5 Sv to tissue and skin.
8. Anonymous – 112: when they (extravasations) do occur in Nuclear Medicine, the volume and radioactivity is pretty low.	8. The volume of the nuclear medicine injection is not an indicator of the activity. Furthermore, as has been shown, even a low amount of radioactivity injected into a small mass of tissue can still result in a relatively high tissue absorbed dose (4).
9. Medical director and nuclear medicine physician, Charlotte, NC – 379: Diagnostic doses are usually very small in volume.	9. See #8 above.
10. ACR 441: While diagnostic extravasation is more common, it would be unlikely if not impossible to meet the §35.3045(b) standard with typical diagnostic nuclear medicine agents.	10. Routinely used diagnostic radiopharmaceuticals emit short-range (non-penetrating) and low-energy x-ray ionizing emissions. When extravasated, localized radiation doses can exceed reporting limits. See # 7 above.

Extravasation causes, symptoms, and biological effects	
Representative statements (comment number)	Fact-based corrections
1. HPS 133: 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	1. The administration though an IV catheter does not directly reduce the risk of extravasation. Extravasation can occur if there have been multiple attempts for initial IV catheter insertion resulting in damage to the vein around the catheter in situ. Easy and free blood aspiration ('blood return") from the IV catheter indicates the catheter is in the vein at the time of aspiration and is an inconclusive assessment tool that should not be solely relied on. If there is damage around or outside the catheter insertion point due to multiple attempts, there could be leakage into the surrounding tissue resulting in an extravasation. Extravasation can also occur if the catheter is displaced with flushing or IV direct administration—when excessive force is used, the catheter tip may "pop out" of (through) the vein if there is not enough catheter length in the vein (catheter purchase in the vein).
2. CNMT in PET Ocala, FL – 23: You have to see the skin raise into a mass or bubble. You have to feel the skin turn from supple to firm.	2. The volume of radiopharmaceutical and saline flush typically injected during diagnostic administrations is unlikely to be large enough to cause swelling, which is only one sign of possible extravasation.
3. CNMT in PET Ocala, FL – 23: Injecting 0.3mL may not produce physical extravasation effects. But after administering 3mL of saline flush, then physical effects of extravasation occur	3. Saline flush may not result in visible swelling and therefore is not a useful indicator of extravasation.
4. Anonymous – 112: If you notice a dose start to extravasate, you stop	4. Due to the low volume of radiopharmaceutical injected, it may be difficult to visually observe or "notice" an extravasation. It is important to check for blood return and ease of flush immediately prior to, during and after injection. Also, diagnostic administrations involve a quick push (sometimes just seconds). If a technologist suspects an extravasation, some or much of the dose can already be in the tissue. Often technologists do not recognize that an extravasation has occurred.
5. Nuclear medicine physician, Emory – 315: If the patient reports pain at the injection site or if swelling is seen, stop the infusion and establish another access site.	5. Radiopharmaceuticals are vesicants capable of causing tissue damage when they escape from the intended vein. Because radiation damages tissue over time, radiopharmaceuticals may not cause an immediate burning sensation at the extravasation site. Therefore, patients may not report pain when extravasated.
6. ACR 441: IV access is secured prior to injection of byproduct material, and sites are observed during and after administrations.	6. Observing the IV access site is necessary but not sufficient. Extravasation will occur where the catheter tip is located, not necessarily right at the catheter insertion site. In addition to #1-4 above, the location of the IV access is also important in order to reduce risk of extravasation. It is important to choose a vein that has adequate length and size to ensure a patent IV catheter. Areas that pose higher risk are the hand, the ante-cubital fossa, and the upper arm. The ideal location is in the forearm, away from area of flexion.

Extravasation causes, symptoms, and biological effects	
Representative statements (comment number)	Fact-based corrections
7. Medical physicist and former member of ACMUI – 479: A number of patient conditions that contribute to patient extravasations resulting in leakage into surrounding tissue and are not the result of a "bad stick" needing regulatory control. Such patient conditions are unpreventable and uncontrollable. These causes of such patient conditions, which could be considered "passive patient intervention", include: Small vein size, Poor vein condition including vein porosity or vein fragility, Venous spasm due to temperature or blood pressure changes, Clot restricting normal venous blood flow, Multiple venipuncture sites, Patient hydration, Patient movement causing needle to accidently exit the vein by either backing out from the point of insertion or puncturing the other side of the vein.	7. The nuclear medicine community and the ACMUI blame the patient for extravasation in nuclear medicine. Yet, these are the same patients who experience extravasation rates that are less than 1% in other intravenous procedures (e.g., chemotherapy and contrast CT administrations) (6-8). In nuclear medicine, there are published papers and previous ACMUI transcripts that specifically highlight that the tools, techniques, and training of technologists contribute to venous access issues and injection processes that cause extravasations (9-11). Furthermore, the Association of Vascular Access is very clear that extravasations are not a patient issue, but under the control of clinicians[1]. The education and training specifically for IV catheter insertion is important for the clinician. Education includes device selection (size and length of catheter), site selection (optimal locations on forearm), prevention, identification, and management of complications.
8. Medical director and nuclear medicine physician, Charlotte, NC – 379: An extravasated dose typically gets absorbed rapidly enough	8. Biological clearance is one determinant of radiation dose (1, 2). High localized doses can occur even when the infusion clears tissue quickly (4). Some radiopharmaceuticals clear slowly. Radiopharmaceutical biological clearance rates are specific to radiopharmaceuticals and to patients. MDP, for example, clears at a much slower rate than FDG.
9. Professor of diagnostic radiology and nuclear medicine physician, University of MD School of Medicine – 14: Most of the extravasated tracers have been subsequently absorbed	9. Just because most of the radiopharmaceutical is eventually absorbed (assuming the commenter meant cleared by the lymphatic system or vascular system) does not mean the tissue did not receive a high dose of radiation prior to clearance (4).
10. Nuclear medicine physician, Emory – 315: Diagnostic radiopharmaceuticals are generally isotonic and iso-pH, usually have no pharmacological effect and the volumes administered are very low.	10. The nature of the pharmaceutical can affect biological clearance. And while the pharmaceutical itself and the overall volume of the radiopharmaceutical may not directly affect patient tissue, the amount of radioactivity extravasated with the pharmaceutical is important in the calculation of the absorbed dose to the tissue (4).
11. CNMT in PET Ocala, FL – 23: It can also be subjective if there was an extravasation or if there is just residual radiopharmaceutical in the vascular and soft tissue.	11. Radiopharmaceutical in the soft tissues defines an extravasation (12).
12. Medical director and nuclear medicine physician, Charlotte, NC – 379: We have never seen a case of physical harm at the injection site due to diagnostic dose extravasation in our institution.	12. Tissue damage caused by radiation injury can take months or years to manifest; skin damage will take days (13). There would be no evidence of skin or tissue damage while a patient is still at the facility. Without identifying and characterizing extravasations and then clinically following patients with significant extravasations for the appropriate amount of time, there is no way to know that harm did not occur (13).

[1] https://www.regulations.gov/comment/NRC-2020-0141-0466, accessed February 23, 2021

Extravasation causes, symptoms, and biological effects	
Representative statements (comment number)	Fact-based corrections
13. Associate professor of radiology, Duke – 369: There is no demonstrable radiological harm to patients from diagnostic extravasations to begin with, so there is nothing to improve.	13. The statement that there is no demonstrable radiological harm is incorrect. In three patients that van der Pol, et. al. stated were followed, all three suffered adverse tissue reactions (13). It is likely that of the remaining 3,013 reported cases of diagnostic extravasations noted by van der Pol et. al., many would have shown demonstrable radiological harm had these patients been followed for the appropriate amount of time.
14. Division Chief molecular imaging and therapeutics, UNC-CH – 253: Classifying extravasation as medical even [sic] would mean that it must be communicated to the patient. Many patients who already have to cope with cancer or other serious diseases would have to deal with this additional piece of information, no matter how trivial it might be.	14. Suggesting that a significant extravasation is a trivial event and patients would have to deal with this additional piece of information is condescending to patients and is diametrically opposed to the practice of modern medicine. Patients have the right to know of incidents that may affect their short and long-term care. A significant extravasation can negatively affect the quality and quantification of the nuclear medicine image (9); the four leading nuclear medicine societies agree with this statement[2]. These images are used to help guide patient care. Furthermore, these same experts admit that a tissue equivalent dose >1.0 Sv can lead to adverse tissue reactions (14).
15. Leading members of SNMMI – 425: If patients are informed that extravasations, as inconsequential as they are, are a "medical event," the impact will be detrimental to nuclear medicine	15. See #14 above. This comment suggests that the nuclear medicine community is more interested in protecting their interest than in being transparent with patients.

[2] https://www.regulations.gov/document/NRC-2020-0141-0156, accessed February 23, 2021

Medical event regulations and the role of federal and state regulators	
Representative statements (comment number)	Fact-based corrections
1. Leading members of SNMMI – 425: Extravasations are a practice-of-medicine issue and thus beyond the scope, appropriately, of NRC regulatory oversight	1. This "practice of medicine" argument ignores the NRC's responsibility to regulate the medical use of byproduct material under the Code of Federal Regulations Title 10, Part 35. Requirements of 10CFR35 provide for the radiation safety of health care workers, the general public, **patients**, and human research subjects in the medical use of radioactive materials by medical centers that hold radioactive material licenses. Section §35.41 deals specifically with procedures for administrations that require a written directive, and licensees must verify that radiopharmaceutical administration are given in accordance with the treatment plan. Naturally, an infusion of radioactive material that localizes within a patient's arm at the injection site will not have been given according to the treatment plan or physician's authorized written directive. Instead, "practice of medicine" is formally defined as "the learned profession that is mastered by graduate training in a medical school and that is devoted to preventing or alleviating or curing diseases and injuries;" whereas any practice that may injure a patient or avoid the effective treatment of disease would be considered the opposite of a legitimate practice of medicine. A radiopharmaceutical extravasation is the unintentional or accidental misadministration of radioactivity to the wrong location. A physician would never intentionally recommend that a patient experience an extravasation. NRC policy on "practice of medicine" is clearly stated in the *Federal Register* 65FR47654, August 3, 2000 (15).
2. HPS 133: 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.	2. Training and experience to correctly administer regulated byproduct materials is clearly addressed in 10CFR35. In this case, the Advisory Committee (ACMUI) position directly contradicts 10CFR35, the Commission's practice of medicine policy, and the NRC's mandate to regulate medical use of byproduct materials for radiation safety of patients.
3. HPS 133: 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 ±20% delivered dose criteria.	3. This ACMUI statement repeated by the Health Physics Society is factually incorrect, as shown by Osborne et al. (4). Subpart M Reporting requirements for medical event reporting are clearly stated under 10CFR35, Subpart M, Subpart M—Reports §35.3045 Report and notification of a medical event.
4. AAPM 440: The threshold dose of 0.5 Sv does not represent any level of patient harm. Accordingly, it should not be required to be reported.	4. Subpart M Reporting Requirements does not require that patients are harmed. The NRC has stated repeatedly: "A Medical Event may indicate potential problems in a medical facility's use of radioactive materials. It does not necessarily result in harm to the patient."
5. CNMT Michigan – 27: Reporting such events will not reduce the number or extravasations nor change the outcome. Us technologists are already committed to doing everything we can to make sure the proper dose is properly administered. Having to go through the tedium of reporting such an event won't make me strive any more than I already do to do the best I can every single time.	5. A clinician's intent or effort are not included as reporting criteria for a medical event (16). The NRC expects that everyone is doing their best to handle isotopes with care, but if a misadministration occurs that exceeds medical event reporting criteria, it should still be reported.

Medical event regulations and the role of federal and state regulators	
Representative statements (comment number)	Fact-based corrections
6. Chief of Division of Nuclear Medicine, UC Davis – 34: technologists already do their level best, usually successfully, to avoid them. To regulate these as medical events would introduce a significant burden of additional work for no obvious medical benefit.	6. See #5 above for technologists trying their best. However, this comment suggests that when extravasations do happen, regulation should not be required because of lack of intent and because having to report a mistake that meets reporting criteria adds work and provides no benefit. Both suggestions ignore specific regulatory requirements under 10CFR35.
7. Medical physicist and former member of ACMUI – 479: The reporting of medical events under §35.3045(a) were created to provide some monitoring that an administration of byproduct material was delivered in accordance with the written directive or physician's imaging protocol. This rationale does not apply to extravasation scenarios because they occur even though the administration proceeded as intended and in accordance with best practices. The NRC would need to create medical event that is contrary to its current stated purpose and redefine purpose of a medical event.	7. The NRC disagrees with the concept that a deviation from a written directive is necessary for medical event reporting. According to NRC guidance[3], a "Medical Event" means an event that meets the criteria in Subpart 35.3045(a). Also, in guidance pertaining to medical event definitions[4], NRC addresses this issue: "Question 65 - Do administrations that do not require a written directive but meet the medical event criteria still need to be reported to the NRC? Yes, criteria for reporting and notification of a medical event in 10 CFR 35.3045 do not require that the administration be one that requires a written directive. Although it is unlikely that a medical event would be associated with a medical use that does not require a written directive, they do happen. For example, diagnostic procedures, which do not require written directives, may meet the medical event reporting criteria and are reportable to the NRC. The criteria requires that a licensee shall report any medical event, except for one that results from patient intervention."
8. APhA 371: proposed limit of 50 rem to affected tissues, an arbitrary dose threshold not related to any known complications.	8. The current reporting limit of 50 rem is not an arbitrary dose threshold. In 2001, the medical event reporting was increased to 50 rem to reflect a more risk-informed approach to reporting. Furthermore, patient harm is not a criterion for medical event reporting. See #4 above. During the proper administration of a radiopharmaceutical, the absorbed tissue dose is about 1 mSv. A 50-rem dose to tissue suggests an accidental misadministration that led to the tissue receiving a dose of about 500 times the normally expected dose.
9. CNMT and RSO, UC San Francisco – 12: Medical events carry an extreme reaction to an event that is infrequent and is already documented.	9. Suggesting the reporting of a medical event carries an "extreme reaction" ignores the NRC's efforts to share learnings to reduce medical events in the future. Extravasations occur frequently across nuclear medicine facilities (9, 17-23). Without a reporting requirement, there is no guarantee extravasations are documented and learnings can be shared.
10. CNMT Michigan – 27: extravasations are already documented (or at least should be) within health systems	10. See #9 above.
11. HPS 133: 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.	11. Without a requirement, there is no guarantee (as evidenced in other public comments) that nuclear medicine facilities will monitor administrations for extravasations, take the appropriate medical interventions, and report these events to the appropriate professionals in the facility.

[3] https://www.nrc.gov/materials/miau/med-use-toolkit/faqs-part35.html#71, accessed February 23, 2021

[4] https://www.nrc.gov/docs/ML2005/ML20055E820.pdf, accessed February 23, 2021

Medical event regulations and the role of federal and state regulators	
Representative statements (comment number)	Fact-based corrections
12. NCHA 336: Professional medical organizations such as The Joint Commission, the Society of Nuclear Medicine and Molecular Imaging and the American College of Radiology have accrediting and reporting programs in place that adequately protect the health and safety of the public. Adding additional reporting to the U.S. NRC is duplicative, as the above-mentioned medical organizations regulate and monitor patient safety standards.	12. Accreditation organizations currently review nuclear medicine; however, no accreditation organization audits radiopharmaceutical administration monitoring programs, administration results, corrective actions, quality improvement efforts, or individual technologist performance. The NRC reporting effort is not duplicative and is an essential part of their responsibility. The NRC is the federal agency responsible for regulating the medical use of byproduct materials and other radioactive substances. The current NRC Medical Use Policy Statement (15) specifically states the NRC is responsible for the accurate administrations of radioactive material and rejects the nuclear medicine profession opinion that the NRC should not protect patients from unintentional doses of radiation.
13. NCHA 336: The very rare infiltrations of therapeutic radiopharmaceuticals that result in actual harm would be included in The Joint Commission's program for reporting "sentinel events."	13. While the Joint Commission Sentinel reporting program does not specifically exclude nuclear medicine extravasations, only external beam radiation events appear in the data[5]. A review of the Sentinel event database found no therapeutic radiopharmaceutical extravasations. Furthermore, a known case of therapeutic radiopharmaceutical extravasation that was associated with patient injury and development of carcinoma (24), was NOT reported as a Sentinel event.
14. Associate professor of radiology, Duke – 369: Accrediting organizations such as The Joint Commission (TJC) require health care facilities to incorporate performance improvement processes of all sorts, and have remedial procedures, such as TJC's "sentinel event" program, to respond to events that harm patients.	14. Accreditation initiatives to encourage quality improvement processes do not ensure there is a focus on radiopharmaceutical administrations. In addition, as noted in #13 above, the Joint Commission Sentinel system does not address radiopharmaceutical extravasations.
15. ACR – 441: Are already addressed through institutional processes, standards and best practices, technologist/personnel IV competency evaluation, and other quality assurance methods.	15. The fact that nuclear medicine extravasation incidence rates are 65 times the rates of contrast CT extravasations suggests that nuclear medicine extravasations are NOT being addressed through institutional processes, standards and best practices, technologist/personnel IV competency evaluation, and other quality assurance methods, as the ACR suggests.

[5] https://www.jointcommission.org/resources/patient-safety-topics/sentinel-event/, accessed February 23, 2021

APPENDIX B

Misrepresentations of Facts, Incorrect Statements, and Incorrect Citations	**Correct Information**
1. Misrepresentation During the 12/8/2020 public comment WebEx (25), Dr. Schleipman (ACMUI Member) suggests that diagnostic radiopharmaceutical extravasations "pose little adverse consequences" and do not warrant reporting. He supports his case by describing a large, multi-center study by Silberstein et. al. (26). He states: "In a more comprehensive prospective study by Silberstein of 11 academic centers submitting characteristics of their radiopharmaceutical administrations and adverse events over a five-year period evaluated over one million radiopharmaceutical administrations, including over 200,000 diagnostic PET studies, over 800,000 diagnostic non-PET studies, and over 13,000 therapeutic procedures. This report concluded that the incidents of radiopharmaceutical adverse events was 2.1 for every 100,000 administrations."	Although Silberstein did conclude that the adverse events incidence rate was relatively low at 2.1-2.3 events per 100,000 dosages, Silberstein excluded several important types of adverse events from his analysis. Specifically, the study excluded altered biodistribution, deterministic and stochastic effects from therapeutic radiopharmaceuticals, poor injection technique, and false positive results from the study's definition of adverse events. **These exclusions include many of the adverse events that result from or relate to radiopharmaceutical extravasations.** Thus, we assert that Dr. Schleipman misrepresents Silberstein's work to support his premise that extravasations pose little risk of adverse consequences.

Misrepresentations of Facts, Incorrect Statements, and Incorrect Citations	**Correct Information**
2. Misrepresentation During the 12/8/2020 public comment WebEx (25), Dr. Jadvar (ACMUI member) stated that "The range of infiltration of 16 percent seems to be taken from a JNMT paper published in December 2019 with the Lucerno company reps as authors. The meta-analysis from EJNMMI publication in 2017, the rate of extravasation is substantially lower at less than one percent.''	Dr. Jadvar misrepresents the authorship of the 2019 JNMT publication (9). While three of the authors of the JNMT paper are Lucerno technical and clinical **resources, the majority of authors are leaders in nuclear medicine.** Authors include: Dr. Terence Z. Wong (Duke), Thad Benefield (UNC), Dr. Shane C. Masters (Wake Forest Baptist), Dr. Jackson W. Kiser and James R. Crowley (Carilion Clinic) Dr. Dustin Osborne (UT Knoxville), Dr. Osama Mawlawi (MD Anderson Cancer Center), Dr. James Barnwell (Wake Radiology), Dr. Pawan Gupta (UCLA), Dr. Akiva Mintz (Columbia), and Dr. David W. Townsend (A*Star-NUS Clinical Imaging Research Centre, Singapore). **In contributing to the paper, all authors attest that the following statements are true**. • Unlike other healthcare injection processes that monitor injection quality (e.g., contrast CT and chemotherapy), there is no evidence PET/CT injections are routinely monitored. • Our project confirmed that by using new technology, centers could routinely monitor injections, establish baseline infiltration rates, and determine center-specific factors that enable quality improvement processes to improve/sustain PET/CT injection infiltration rates. • Seven centers and 56 technologists provided data on 5,541 injections. The centers' aggregated baseline infiltration rate was 6.2% (range 2% - 16%). Based on their specific associative factors, four centers developed improvement plans and reduced their aggregated infiltration rate from 8.9% to 4.6% ($p<0.0001$). On-going injection monitoring showed sustainability. Significant center- and technologist-level infiltration rate variation was found ($p < 0.0001$ and $p= 0.0020$). Furthermore, Dr. Jadvar misrepresents the nuclear medicine extravasation rate. In their EJNMMI 2017 publication, van der Pol, et al., did not report the rate of extravasations; instead, they reported the percent of patients with diagnostic extravasations who were followed clinically.

Misrepresentations of Facts, Incorrect Statements, and Incorrect Citations	**Correct Information**
3. Misrepresentation, Incorrect Statement, and Incorrect Citation. In their written public statements regarding the petition[6], the American College of Radiology (ACR), Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American Society of Nuclear Cardiology (ASNC), and the American College of Nuclear Medicine (ACNM) suggest the potential for tissue harm from diagnostic radiopharmaceutical extravasations is insignificant. In each case, they also reference the van der Pol paper. (13) They state: "A study into reports of extravasation found that less than 0.001 percent of diagnostic nuclear medicine extravasations result in temporary symptoms of any kind" and "of a total of 3,016 diagnostic radiopharmaceutical extravasations, only three (<0.1%) were associated with adverse reactions."	As noted in Example 2, the van der Pol (2017) paper suggests that an institutionalized lack of monitoring for extravasations in nuclear medicine exists—of the 3,016 diagnostic radiopharmaceutical extravasations reported in the literature, only three reported dosimetry and patient follow-up (0.1%, not 0.001%). All three patients suffered adverse tissue reactions, occurring 20 days, 2 years, and 3 years after the extravasation (13). Of the remaining 3,013 diagnostic extravasations reviewed in the paper, none reported dosimetry performed or patient follow-up. Had any of these 3,013 extravasation cases had dosimetry performed and been followed, it is reasonable to expect other injuries would have been found. The societies and their leading members also incorrectly cite and misrepresent the van der Pol (2017) paper when they suggest that the harm caused by diagnostic extravasations is insignificant. Their statements are also incorrect.
4. Misrepresentation In their written public statement regarding the petition[7], the Health Physics Society (HPS), while referring to the need to characterize an extravasation, wrote "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."	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.
5. Incorrect Statement In their written public statement regarding the petition[8], the ACR compared contrast media and chemotherapeutic administrations to nuclear medicine administrations as follows: "They are not analogous to administrations of radiopharmaceuticals, which are typically small volume, without inherent properties harmful to tissues, and-particularly with diagnostic nuclear medicine and molecular imaging agents often administered by direct push by highly trained staff operating in a culture of safety."	This ACR statement is incorrect. It is known that the ionizing properties of radioactivity from radiopharmaceuticals are inherently harmful to tissue (14).

[6] https://www.regulations.gov/comment/NRC-2020-0141-0428, accessed February 23, 2021
[7] https://www.regulations.gov/document/NRC-2020-0141-0137, accessed February 23, 2021
[8] https://www.regulations.gov/comment/NRC-2020-0141-0444, accessed February 23, 2021

Misrepresentations of Facts, Incorrect Statements, and Incorrect Citations	**Correct Information**
6. Incorrect Citations In their written public statement regarding the petition[9], the HPS suggested nuclear medicine extravasations are infrequent and wrote: "Extravasation is estimated to occur in 0.6% to 6% of radiopharmaceutical administrations."	In its position statement, HPS incorrectly cited two references, neither of which is relevant. The first reference (13) is an article regarding the consequences of radiopharmaceutical extravasations. This reference states that radiopharmaceutical extravasations are frequent but does not indicate a rate. The second reference (27) cited by HPS is not a radiopharmaceutical reference, but rather a reference for the chemotherapy extravasation rate. This reference states that **the chemotherapy extravasation rate is between 0.6% and 6%**. A thorough literature review of retrospective nuclear medicine imaging studies shows the radiopharmaceutical extravasation rate is 15.5% (9, 17-23). The high frequency of radiopharmaceutical extravasations is also supported in two transcripts from the ACMUI meetings held on the extravasation topic in 2008 and 2009 (10, 11). Members of the ACMUI reported that extravasations were a frequent occurrence. Furthermore, during the October 14, 2020 FDA-NRC Workshop: Enhancing Development of Emerging Technologies – Radiopharmaceuticals and Radiological Devices (28), the FDA also confirmed that extravasations are a common occurrence . Finally, in the SNMMI, ACNM, and ASNC public comment, these societies acknowledged that extravasations occur frequently. Thus, the HPS incorrectly cited published papers to support a point that is contradicted by dispositive evidence.
7. Incorrect Statement In their written public statement regarding the petition[10], the American Association of Physicists in Medicine (AAPM) wrote: "Quantitative imaging is not used in clinical nuclear medicine" and "there is no current clinical role for quantitative imaging in nuclear medicine."	Dr. Daniel Sullivan, the founder of the Radiology Society of North America's Quantitative Imaging Biomarker Alliance, describes in public comment 202[11] many instances of how quantitative imaging is used in clinical nuclear medicine. For example, Dr. Sullivan quoted the ACR's publication, "Diagnostic Imaging 2018 Quality Measures" (29), that states "providing an accurate SUV result for every cancer patient is an expected performance measure by the American College of Radiology." These AAPM statements are categorically false.

[9] https://www.regulations.gov/document/NRC-2020-0141-0137, accessed February 23, 2021
[10] https://www.regulations.gov/comment/NRC-2020-0141-0443, accessed February 23, 2021
[11] https://www.regulations.gov/document/NRC-2020-0141-0206, accessed February 23, 2021

Misrepresentations of Facts, Incorrect Statements, and Incorrect Citations	**Correct Information**
8. Incorrect Statement In perhaps the most concerning statement from their written public comment regarding the petition, the AAPM states: "The bulk of the supporting materials provided in Appendix 1 of the petition from Lucerno are from 18F-FDG imaging. A nominal injected amount of radioactivity in 18F-FDG imaging is 370 MBq, which has an effective dose of 7 mSv (nominal). This is two orders of magnitude (i.e., 100x) less than the proposed threshold of 500mSv."	The AAPM statement is incorrect. A 370 MBq injection of FDG results in a nominal 7 mSv whole body dose, *assuming uniform dose distribution*. However, when an extravasation occurs and radioactivity localizes in a small volume of patient tissue at the injection site, the absorbed dose to the tissue can easily exceed medical event reporting limit of 500mSv and thresholds that can lead to adverse tissue reactions (4).
9. Misrepresentation In their written public comment regarding the petition, leading members of the SNMMI[12] conclude that "Monitoring is not expected to improve administration techniques."	One of these members is a co-author of a poster (attached on the following page) presented at a recent SNMMI meeting. The poster describes a quality improvement effort enabled by monitoring technology. By monitoring administrations, this center discovered their extravasation rate was 12.8%. Their data analysis showed high level of variation in extravasation rates and venous access methods among technologists. The center put improvement plans in place. One technologist was asked to stop using butterfly venous access and their extravasation rate dropped from 16% to 0%. However, when the technologist believed the project was over, they returned to butterfly use and their rate jumped to 13%. The center concluded: "We found that PET dose extravasation rates **decreased after active monitoring** and educational practices were implemented. Our study shows, however, that **ongoing monitoring may be useful as technologist practice patterns and infiltration rates can fluctuate over time**." The public comment from this SNMMI leader contradicts the scientific poster that they co-authored.

[12] https://www.regulations.gov/comment/NRC-2020-0141-0476, accessed February 23, 2021

Improving the quality of PET radiopharmaceutical injections: Our lessons learned

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Objectives

Quality improvement efforts in nuclear medicine seek to reduce errors and variations in care due to our human nature. In our clinic, we embarked on a quality improvement project to analyze and implement change to reduce the extravasation rate of PET injections. This is important to ensure the proper dose is administered, obtain the best quality images, reduce artifacts, and to allow for the most optimal quantitative analysis.

Methods

A plan-do-study-act (PDSA) cycle process was conducted as follows:

1) **Plan**: The number of extravasated PET doses seemed unacceptably high during clinical readouts. The objective of this study was to gain an understanding of the actual number of extravasations and the parameters associated with successful and unsuccessful injections.

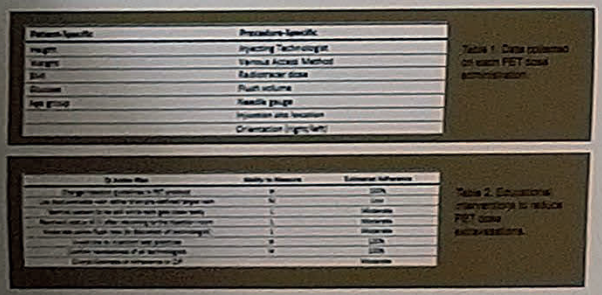
2) **Do**: Data was recorded regarding extravasation (yes/no), patient characteristics, injecting technologist, venous access method (IV, butterfly, direct syringe injection), needle gauge, injection site and side, and flush volume.

3) **Study**: Statistical analysis of data with critical evaluation.

4) **Act**: Implement educational program and changes to PET injection methods based on study data. After that, the overall infiltration rate was reassessed.

Results

Our data analysis showed high levels of variation among technologists in extravasation rates, venous access methods, needle gauge, injection side and site, and flush volume among technologists. It also showed that some technologists used a predetermined injection site despite patient characteristics (i.e., "preferred vein" vs. "best vein"). After an educational intervention including an in-service on injection best practice, analysis was repeated and showed improvement in extravasation rates.



Conclusion

In our study, the plan-do-study-act cycle resulted in an initial decrease in PET dose extravasation rates. Ongoing analysis could help determine if this QI initiative continues to have positive results, the optimal time for in-service training repetition, and to assist technologists in maintaining optimal injection techniques.

Introduction

In our institution's PET/CT department, we embarked on a quality improvement project to decrease the number of PET radiotracer extravasations. Dose extravasation compromises the final PET images in several ways: SUV values will be abnormally low, reconstruction artifacts create photopenia around the injection site (which may or may not be in the field of view), 3D image reconstructions are often unreadable, and extravasated tracer can travel through the lymphatic system, causing uptake in lymph nodes, which can be confused with cancer.

Quality Improvement Project:

PET dose extravasation analysis

PLAN: The number of extravasated PET doses seemed unacceptably high during clinical readouts. The objective of this study was to gain an understanding of the actual number of extravasations and the parameters associated with successful and unsuccessful injections. Our department decided to study extravasation rates and injection parameters in attempt to better understand this problem.

DO: PET injections were monitored during 11 weeks in 2017. Data was recorded regarding extravasation (yes/no), patient characteristics, injecting technologist, venous access method (IV, butterfly, direct syringe injection), needle gauge, injection site and side, and flush volume. An extravasation-detection device (LARA System, Lucerno Dynamics, LLC, Cary, NC) was used to determine if extravasation occurred. This quality improvement project did not require institutional review board approval.

STUDY: 469 injections were monitored during the 11-week study period. This was 84% of all PET injections during this time. Model-based analysis (SAS v. 9.4) and technologist input were used to identify potential contributing factors.

The infiltration rate was 12.8% (SE 1.6%, 95% CI 9.94, 16.24). Analysis revealed a significantly higher predicted probability of infiltrations for right-side injections (13.5%) compared to left-side injections (5.5%).

Predicted probability of infiltration was not significantly different among the technologists; however, technologist-specific differences in injection practices were observed. For example, one technologist had a 16% infiltration rate and was using butterflies to administer the radiopharmaceutical. This infiltration rate decreased to 0% once IV access was utilized, evidenced in a follow-up study and analysis. However, this improvement and use of IV access was not sustained. (See Analysis After Educational Intervention, next column.)

ACT: An educational intervention was implemented. Approved injection guidelines in the PET protocol book were updated. An educational session was attended by the technologists, with the following guidelines:

1. Use best available vein after evaluating patient rather than predefined target vein per technologist preference.
2. Remind patient to be still while the dose is being readied.
3. Use IV access. No butterflies or straight sticks.
4. Recheck status of IV just prior to radiopharmaceutical administration.
5. Use a moderate saline flush rate.

Analysis After Educational Intervention

An additional 469 PET injections were monitored in a similar fashion to the initial study and data and were analyzed in a similar fashion. Adherence to quality improvement measures was assessed. Technologist data were evaluated. After this, 2322 injections were monitored in a similar fashion to see if results were sustainable.

Analysis of three technologist infiltration rates over time (See Graph, below.)

Technologist A

Technologist A had a 16% infiltration rate and was using butterflies to administer the radiopharmaceutical. This infiltration rate decreased to 0% once IV access was utilized, evidenced in the follow-up study and analysis. After this improvement was seen, however, Technologist A had an increase in extravasation rate to 13%, which was similar to the initial infiltration rate. Upon review of the data, Technologist A had returned to using butterflies for radiopharmaceutical injection.

Technologist B

Technologist B began with a 17% infiltration rate, decreased to 9% after the initial educational intervention, and continued to decrease to 3% in the long-term analysis to assess if improvement in infiltration rate was sustainable.

Technologist C

Technologist C had the lowest infiltration rates throughout the study (0%, 3%, 1%). Technologist C adhered to best injection protocol practices in the course of personal professional practice, and continued to practice these throughout the study.

Conclusion

Our PET/CT center reduced infiltration rates through our plan-do-study-act quality improvement project. We found that PET dose extravasation rates decreased after active monitoring and educational practices were implemented. Our study shows, however, that ongoing monitoring may be useful as technologist practice patterns and infiltration rates can fluctuate over time.

REFERENCES

1. Esser J. Procedure Guidelines Nuclear Medicine: Kloosterhof Neer BV; 2017.
2. Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature. J Nuc Med. 2009;50.
3. Smith EM, Harris CC, Rohrer RH. Calculation of Local Energy Deposition Due to Electron Capture and Internal Convension. J Nucl Med. 1966;7(1):23-31.
4. Osborne D, Kiser JW, Knowland J, Townsend D, Fisher DR. Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements. Health Phys. 2021.
5. Hioki T, Gholami YH, McKelvey KJ, Aslani A, Marquis H, Eslick EM, et al. Overlooked potential of positrons in cancer therapy. Sci Rep. 2021;11(1):2475.
6. Jackson-Rose J, Del Monte J, Groman A, Dial LS, Atwell L, Graham J, et al. Chemotherapy extravasation: establishing a national benchmark for incidence among cancer centers. Clin J Oncol Nurs. 2017;21(4):438-45.
7. Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR. Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections. Radiology. 2007;243(1):80-7.
8. Dykes TM, Bhargavan-Chatfield M, Dyer RB. Intravenous contrast extravasation during CT: a national data registry and practice quality improvement initiative. J Am Coll Radiol. 2015;12(2):183-91.
9. Wong TZ, Benefield T, Masters S, Kiser JW, Crowley JR, Osborne D, et al. Quality Improvement Initiatives to Assess and Improve PET/CT Injection Infiltration Rates in Multiple Centers. J Nucl Med Technol. 2019;47:326-31.
10. Official Transcript of Proceedings, Advisory Committee on the Medical Uses of Isotopes. US Nuclear Regulatory Commission; 2008.
11. Official Transcript of Proceedings, Advisory Comittee on the Medical Use of Isotopes. US Nuclear Regulatory Commission; 2009.
12. Helm RE, Klausner JD, Klemperer JD, Flint LM, Huang E. Accepted but unacceptable: peripheral IV catheter failure. J Infus Nurs. 2015;38(3):189-203.
13. van der Pol J, Voo S, Bucerius J, Mottaghy FM. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. Eur J Nucl Med Mol Imaging. 2017;44(7):1234-43.
14. Siegel JA. Guide for Diagnostic Nuclear Medicine: Society of Nuclear Medicine; 2002.
15. Nuclear Regulatory Commission - Medical Use of Byproduct Material; Policy Statement, Revision. Federal Register; 2000. p. 47654-60.
16. Code of Federal Regulations, 10 CFR § 35.3045, Subpart M - Report and notification of a medical event.
17. Hall N, Zhang J, Reid R, Hurley D, Knopp M. Impact of FDG extravasation on SUV measurements in clinical PET/CT. Should we routinely scan the injection site? J Nucl Med. 2006;47(suppl 1):115P.
18. Bains A, Botkin C, Oliver D, Nguyen N, Osman M. Contamination in 18F-FDG PET/CT: an initial experience. J Nucl Med. 2009;50(supplement 2):2222.
19. Krumrey S, Frye R, Tran I, Yost P, Nguyen N, Osman M. FDG manual injection verses infusion system: a comparison of dose precision and extravasation. J Nucl Med. 2009;50(supplement 2):2031.
20. Osman MM, Muzaffar R, Altinyay ME, Teymouri C. FDG dose extravasations in PET/CT: frequency and impact on SUV measurements. Front Oncol. 2011;1:41.
21. Silva-Rodriguez J, Aguiar P, Sanchez M, Mosquera J, Luna-Vega V, Cortes J, et al. Correction for FDG PET dose extravasations: Monte Carlo validation and quantitative evaluation of patient studies. Med Phys. 2014;41(5):052502.
22. Muzaffar R, Frye SA, McMunn A, Ryan K, Lattanze R, Osman MM. Novel method to detect and characterize (18)F-FDG infiltration at the injection site: a single-institution experience. J Nucl Med Technol. 2017;45(4):267-71.
23. McIntosh C, Abele J. Frequency of Interstitial Radiotracer Injection for Patients Undergoing Bone Scan. The Canadian Association of Radiologists; April 15, 2016; Montreal, Quebec2016.

24. Benjegerdes KE, Brown SC, Housewright CD. Focal Cutaneous Squamous Cell Carcinoma Following Radium-223 Extravasation. Proc Bayl Univ Med Cent. 2017;30(1):78-9.
25. Official Transcript of Proceedings, Public Comment Meeting on Radiopharmaceutical Extravasations. US Nuclear Regulatory Commission; 2020.
26. Silberstein EB. Prevalence of adverse events to radiopharmaceuticals from 2007 to 2011. J Nucl Med. 2014;55(8):1308-10.
27. Jordan K, Grothe W, Schmoll HJ. Extravasation of chemotherapeutic agents: prevention and therapy. Dtsch Med Wochenschr. 2005;130(1-2):33-7.
28. Official Transcript of Proceedings - Enhancing Development of Novel Technologies: Radiopharmaceuticals and Radiological Devices FDA-NRC Workshop. Nuclear Regulatory Commission; 2020.
29. Diagnostic Imaging 2018 - Quality Measures. American College of Radiology; 2018.