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Reporting Nuclear Medicine Injection Extravasations as Medical Events

Comment On: NRC-2020-0141-0004
Reporting Nuclear Medicine Injection Extravasations as Medical Events; Notification of Docketing and Request for Comment

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General Comment

See attached file(s)

Attachments

2020-11-30 Public Comment Final

Wake Forest Baptist Results Poster

Townsend_Letter_ACMUI

This comment is in reference to Docket ID NRC-2020-0141.

The essence of the petition is simple. It is based on three straightforward premises: extravasations are avoidable, the NRC has jurisdiction to regulate them, and they can meet medical event reporting criteria.

1. Avoidable extravasations

Federal regulations governing the use of medical isotopes require medical events to be reported. Extravasation of diagnostic and therapeutic radiopharmaceuticals can meet the reporting criteria, but because of a 1980 NRC policy, all extravasations are exempted from reporting.

Based on the original intent of the reporting regulations—to learn from misadministrations and reduce their frequency—the NRC saw no reason to require reporting of extravasations since they had been told that extravasations were a frequent occurrence in intravenous and intra-arterial administrations and were "virtually impossible to avoid."

The petition cites robust, dispositive evidence that extravasations are avoidable, and therefore extravasations that meet reporting criteria should be reported.

2. Jurisdiction

The current NRC Policy Statement on the Medical Use of Radioactive Materials supports the reporting of extravasations. When the NRC modified this Statement in 2000 a press release followed. Here is an excerpt from that release:

> "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." **This statement makes clear that the focus of NRC regulation is primarily on ensuring that physician's directions, as they pertain to the administration of radiation or of NRC-regulated radioactive material, are followed.**

The Federal Register (August 3, 2000) was more specific in response to questions about the NRC role in ensuring accurate delivery of radioactive material and the need to protect patients:

> The Commission has a role in assuring accurate delivery of radiation doses and dosages to patients and rejected the notion that the NRC should not regulate patient radiation safety (44 FR8243 February 9, 1979). The 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 primary responsibility for the protection of their patients. However, NRC's role is also necessary to ensure radiation safety of patients."

Depositing a portion of the radiopharmaceutical into the tissue instead of the vein is the very definition of inaccurate delivery.

3. Medical event criteria

Subpart M—Reports, 10 CFR Part 35 specifies criteria for reporting and notification of medical events. Extravasations are covered in the regulations.

(a) **A licensee shall report any event as a medical event**, except for an event that results from patient intervention, **in which**—

(1) **The administration of byproduct material or radiation from byproduct material**, except permanent implant brachytherapy, **results in**—

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

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

Some diagnostic and therapeutic radiopharmaceuticals, when infiltrated into soft tissue instead of venous administration as intended, can exceed 0.5 Sv (50 rem) to tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin.

These current reporting requirements and limits were implemented in 2002 as part of the Commission's overall strategy to decrease oversight of certain nuclear materials that pose the lowest radiological risks and strengthen the emphasis on those materials or processes posing higher risk. Reporting limits were increased to the 50-rem threshold as part of the effort to ensure patient protection was more risk-informed. The term "misadministration" was also changed to "medical event" as an effort to disconnect reporting terminology from medical error connotation. Furthermore, the NRC made it clear that a "medical event" may not mean a patient has been harmed. The NRC website specifically addresses this issue:

> "…a 'medical event' indicates potential problems in a facility's use of radioactive material. It does not necessarily result in harm to a patient. But the NRC's rules are designed so events are reported to the NRC and the public."

Since extravasations are avoidable and can exceed medical event reporting limits, there are no legitimate reasons that significant unintentional irradiation of patient tissue from extravasations should be handled any differently than other medical events.

There are additional compelling reasons for reporting of significant extravasations. Extravasations can cause patient harm and should be reduced. Performing dosimetry and following patients will improve understanding of energy deposition and the mechanism/timing of radiation injury to tissue. And patients have a right to know when a medical event affects them.

1. Patient harm

Diagnostic nuclear medicine procedures are very low risk and provided great patient benefit when radiopharmaceuticals are administered properly. However, extravasating a diagnostic dose changes the risk-benefit profile. Not all diagnostic extravasations will harm patients, but some will.

The four leading nuclear medicine societies have affirmed in a public statement that diagnostic extravasations are frequent and can affect image quality and quantification. Because of imaging protocols, injection sites are often outside the imaging field of view in many nuclear medicine studies.

Because nuclear medicine extravasations are unique in their detection difficulty, because their frequency is not monitored, because many if not most extravasated imaging studies are NOT repeated, and because interpreting physicians can be unaware of instances of extravasation, it is possible that compromised images are being used to guide patient care. The petition cites at least 50 clinical references of how diagnostic radiopharmaceutical extravasations can or have affected images and possibly patient care. Dr. David Townsend and Dr. Dan Sullivan, two of the leading experts in image quality and quantification, have clearly confirmed this position in recent articles (https://arrsinpractice.org/precision-prospectus-limiting-variability-in-pet-interpretation/ https://arrsinpractice.org/extravasation-reporting-the-scientific-case-for-regulatory-change/) and in their public comments to the NRC or the Advisory Committee on the Medical Uses of Isotopes in 2019.

Diagnostic radiopharmaceutical extravasations can also result in radiation doses that not only exceed the medical event reporting limit of 0.5 Sv, but also the threshold of 1.0 Sv that the nuclear medicine profession proposes as a threshold that can lead to adverse tissue reactions. Again, not all extravasations are going to exceed these limits, but many do. Lucerno has provided the NRC with 36 examples of significant extravasations of either 18F-FDG or 99mTc-MDP that resulted in high doses to the tissue. The dosimetry methods used to calculate these doses are not ultra-conservative approaches that would provide worse case scenarios. These methods employ patient-specific biological clearance information along with conservatively large, affected tissue volumes (patient-specific or reference volumes) to produce fast and accurate estimates of tissue dose.

Therapeutic radiopharmaceutical extravasations can cause patient harm. While less frequent than diagnostic extravasations in many facilities (due to the extra attention paid by licensees to the therapy administrations), therapeutic extravasations can certainly exceed reporting criteria and adverse tissue reaction thresholds. The literature is also clear regarding tissue harm from therapies. In addition to acute harm, a therapy extravasation results in the prescribed dose not reaching the intended target.

2. Understanding radiopharmaceutical safety

ACMUI members, the nuclear medicine societies, individual commenters, and shockingly, the Health Physics Society have all publicly stated that diagnostic extravasations do not or will not cause patient harm. Many have said that it is not possible for diagnostic extravasations to result in a tissue dose that exceeds the reporting limit. This may be the result of the community's long-term messaging to patients that the low doses of diagnostic radiopharmaceuticals will not result in appreciable doses. However, this messaging assumes proper and complete administration of the radiopharmaceutical. But to deny that diagnostic extravasations can in fact result in significant localized dose is disingenuous and concerning.

One possible explanation for these comments is a lack of awareness of the emission energy of positrons, conversion electrons, Auger electrons, and low-energy photons that are deposited within millimeters of the decaying radioactive atoms. But the physics of energy deposition is clear regarding extravasations—all of the non-penetrating emission energy from the extravasated radiopharmaceutical is deposited locally in the tissue. This energy is not being deposited systemically and it cannot be ignored.

Another possible explanation for this lack of knowledge is that dosimetry is not being routinely performed for extravasations. This fact is clearly captured in the often-misquoted van der Pol et al. literature review. The authors cited that only 3 diagnostic extravasations had dosimetry performed out of 3,016 reported cases. All three resulted in adverse tissue reactions over time—discovered only

because the patients were followed long term. Many commenters mentioned they do not see harm, an argument which reveals a lack of understanding regarding when patient harm would become evident. A Division Chief of Molecular Imaging and Therapeutics noted that patients see a referring physician 1-14 days following a diagnostic or therapeutic procedure, "a time frame in which any tissue damage associated with extravasation would have taken place." Other comments by nuclear medicine professionals also suggests a lack of awareness how long it can take (sometimes many months or 2-3 years) for radiation injury to patients to become apparent. One public comment by a radiation biologist with a specialty in radiation toxicity to tissue got this correct.

Furthermore, some comments demonstrate a misunderstanding regarding skin dose. Even extravasations that result in a high *tissue* dose may not lead to a dose to the *overlaying skin* sufficient to cause visible symptoms. This is because the non-penetrating emissions tend to absorb into tissue before reaching the skin.

3. Informing patients

The previously mentioned Division Chief also commented that classifying significant extravasations as medical events would require notifying the patient. The Division Chief suggests that patients are already coping with cancer or other serious diseases and would "have to deal with this additional piece of information, no matter how trivial it might be." These comments are completely inconsistent with the current healthcare tenets of transparency, patient participation in their care, and patient rights. It is disturbing to think that some nuclear medicine professionals would characterize an extravasation of 10 mCi of 18F-FDG or 15 mCi of 99mTc-MDP, for example, as a "trivial event" and then not inform the patient.

In conversations with over 50 oncologists, only one was aware of the term "nuclear medicine extravasations." An article from University of Tennessee Knoxville found a very small percentage of radiology reports noted extravasation, even when the radiologists were aware of an extravasation. That same paper reported that once prospective injection quality monitoring began at the center, reports of extravasations improved to 100%. The lack of reporting to referring physicians suggests that patients are informed even less frequently.

Reporting of significant extravasations would ensure that patients and their referring physicians are made aware of the medical event. This would allow the patient and their physician, in consultation with the nuclear medicine clinician, to determine if the procedure should be repeated. Additionally, the patient and referring physician will be aware of tissue damage that may result and the approximate time for symptoms to appear.

Reporting significant extravasations will lead to extravasation dose characterization, will drive quality improvement, and will benefit patients.

Several commenters have espoused arguments against the reporting of extravasations that exceed medical event criteria. These include administrative burden, self-regulation, claims of passive patient intervention, suggestions the NRC is intruding in the practice of medicine, and a lack of resources, to name a few.

1. Expected reporting burden

For centers that rarely extravasate, the reporting burden will be minimal. For those that routinely extravasate, process improvements will be made, and then reporting burden will be minimal for them as well.

For example, one center was routinely extravasating approximately 13% of their 2,000 annual PET/CT injections. Process improvements were implemented, and today they extravasate less than 2% of the time. They believe that they have prevented between 100-150 significant extravasations in the past 3 years as a result of their improvement effort. Since January 2020, this center has performed dosimetry on 5 cases of extravasation. One case resulted in a dose that would exceed reporting limits. For proactive long-term follow-up, this patient was added to the internal process used to follow fluoroscopy-guided intervention patients experiencing high skin doses.

For improved centers, ongoing monitoring efforts and dosimetry work is not the long-term burden feared by the community. Furthermore, rulemaking could help ensure that the ongoing reporting burden for centers that demonstrate they are striving to improve their processes would be minimal. This would allow regulators to focus on licensees that do not have their administration of radiopharmaceuticals under control.

2. The argument for self-regulation

The nuclear medicine community has been against regulatory reporting since the late 1970s. This reluctance is documented in the Federal Register when the 1980 misadministration regulation went into effect. In fact, a nuclear medicine physician proudly told me and my colleague that they were personally responsible for persuading the NRC in 1979 that extravasations are virtually impossible to avoid. A public comment by Dr. Carol Marcus shows how this influence continued in early 1990s, when she states that she ensured the reporting exemption continued to remain in the regulatory language. The 2008 and 2009 ACMUI meeting transcripts clearly state that even though the members knew extravasations were frequent, knew they could be improved, and knew that they could exceed reporting limits, the members recommended to retain the exemption because they did not want the administrative burden of reporting. The 2019 ACMUI, when faced with new evidence that extravasations are avoidable, still claimed extravasations could not be prevented and then suggested extravasations were the patient's fault. More recent public comments are suggesting that extravasations are a practice of medicine issue and the NRC should not intrude into this issue. The hundreds of public comments supporting these previous positions suggest that the community will continue to minimize this issue and that no substantive improvement is forthcoming unless changes are mandated.

3. Passive patient intervention and practice of medicine

In 2020, we know that extravasations can be avoided. We know that the ACMUI proposal of a new excuse not to report extravasations, "passive patient intervention," is farcical. Attached is a poster presented at a recent SNMMI/ACNM mid-winter meeting that clearly shows extravasations are not the fault of patients. By modifying tools and techniques, and by increasing technologist training, extravasation rates were reduced. Later, when the process improvements were ignored by a technologist, extravasations returned to previous rates. Furthermore, the suggestion that extravasations that result in doses that exceed reporting limits are not a regulatory issue but instead a practice of

medicine issue, or that the NRC would be intruding into medical judgments, should be categorized similarly to the "passive patient intervention" excuse. There is no clinical evidence that an extravasation helps a patient. No clinician is ever going to intentionally extravasate a patient. No clinician is ever going to claim that in their best judgement an extravasation is warranted during the administration of a radiopharmaceutical. Clearly, *administering* radiopharmaceuticals is a practice of medicine. However, *misadministration* of these same radiopharmaceuticals can exceed the reporting limits and should be reported. NRC regulations in no way prevent or intrude on the practice of medicine. They do, however, ensure that patients are being protected.

4. Limited resources

Some members of the community claim that monitoring injections and reporting of extravasations will lead to increases in required training and technology. They argue that quality improvement efforts will take time and financial resources that are not available. Yet, the same efforts and resources would be needed for centers to fix the extravasation issue on their own. Other commenters claim that because they do not have all the right resources, they cannot be expected to report extravasations.

To ensure the radiation safety of each patient, nuclear medicine extravasations must be identified and then mitigated as soon as possible. Furthermore, they should be characterized to assess the impact to the image and the patient. Based on the community's historical reluctance to report medical events and their circular logic regarding resources, mandated reporting is required.

Summary

Members of the nuclear medicine community currently report medical events that exceed well-defined reporting criteria. An extravasation that meets the criteria should also be reported now that we know the exemption policy is incorrect. Resistance to change is natural and expected, but that is not a valid reason to retain the status quo. I encourage the NRC to study the evidence and accept the petition.

I also encourage the NRC to grant a 12-month grace period to allow for planning and implementation of quality improvement efforts in order to reduce the frequency of extravasations before reporting is required. Furthermore, the NRC should consider rulemaking to simplify reporting requirements for centers actively monitoring administrations, tracking improvements of extravasation rates, characterizing extravasations, and following patients who exceed reporting limits.

Thank you for considering these comments.

Ron Lattanze

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

Dear Dr Palestro,

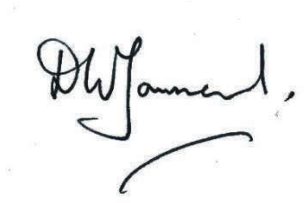
I am writing to you as co-inventor of the combined PET/CT scanner (along with Dr Ronald Nutt) that brought PET scanning into mainstream radiology for imaging oncology patients. The device became commercial in 2001 and now there are around 5000 such scanners worldwide. Over two million PET/CT scans are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

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

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

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

Sincerely,



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Improving the quality of PET radiopharmaceutical injections: Our lessons learned

Wake Forest School of Medicine

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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.

Patient-Specific	Procedure-Specific
Height	Injecting Technologist
Weight	Venous Access Method
BMI	Radiotracer dose
Glucose	Flush volume
Age group	Needle gauge
	Injection site location
	Orientation (right/left)

Table 1. Data collected on each PET dose administration.

[illegible]	Ability to Measure	Estimated Adherence
[illegible]	[illegible]	[illegible]

Table 2. Educational interventions to reduce PET dose extravasations.

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

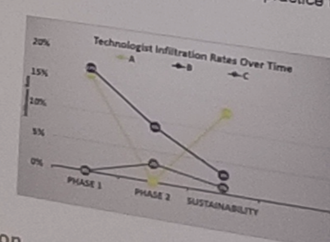
Technologist A had a 16% infiltration rate and was using butterflies to administer the radiopharmaceutical. This infiltration rate decreased to 0% once IV access was utilized, evidenced in the follow-up study and analysis. After this improvement was seen, however, Technologist A had an increase in extravasation 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.