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Reporting Nuclear Medicine Injection Extravasations as Medical Events

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General Comment

Thank you for requesting input from the public on this topic. I have feedback regarding the proposed change to § 35.3045, "(3) The administration of byproduct material results in an extravasation that requires medical attention for a suspected radiation injury." If I am interpreting the rule correctly, medical event reporting would only be required for suspected radiation injuries if medical attention ("any techniques used to reduce the chance, severity, or symptoms of a suspected radiation injury.") is provided.

During the NRC's public meeting on May 24, 2023, a commenter supposed that nuclear medicine practitioners may forego injecting higher risk patients out of fear they would tarnish their track record of having no reported medical events. While admittedly sardonic, if that sort of fear mongering is to be believed, then one must assume practitioners would also choose to withhold medical attention following extravasation to similarly protect their reputations. Personally, I believe both courses of action would be unthinkable; clinicians take patient care very seriously.

Notwithstanding the proposed “medical attention” requirement, the proposal to base medical event reporting on suspicion of injury is by itself an unjustifiable deviation from established dose-based thresholds. The drastic change in regulatory stance would create a precedent in conflict with all other medical event reporting requirements. Will instances of the wrong radionuclide being administered now be subjected to the same injury threshold? What about administration to the wrong individual or to a fetus?

The logical solution is to treat extravasations the same as any other event—if unintended dose to tissue or skin exceeds 50 rem, then it is reportable. NRC has been correct in establishing quantitative dose thresholds, and requirements based on subjective or qualitative metrics will only cause confusion.

I am writing in response to the preliminary proposed rule language on the reporting of nuclear medicine injection extravasations as medical events. NRC is seeking to obtain input from stakeholders and has specifically asked for feedback regarding 14 questions. My comments here are in response to others and are intended to help ensure clarity and transparency in the discussions.

In public comment 30, a summary is given of a recently published paper entitled "Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose" by Sunderland, et. al. I think it is important for NRC staff to recognize that this paper contains several problems which raise questions about the validity of its conclusions. Specifically, the paper's methods are not well described, its results contain errors, and the peer-review process appears to have lacked rigor. I will briefly summarize the problems here, but a detailed response letter has been reviewed and accepted for publication by Frontiers in Nuclear Medicine (see attached).

The paper contains methodology problems.

- Insufficient detail is given as to the selection criteria for the studied imaging centers.
- Dosimetric methods were used which may neglect dose to the underlying muscle by focusing on subdermal and dermal tissues only.
- It is not clear whether appropriate corrections were made during calculation of the initially extravasated activity.

Data and values are inconsistent or contradict those presented elsewhere within the paper.

- The dimensions of assessed tissue are not consistent.
- Units identified in figures do not match those given in the text.
- Figure axes and captions are contradictory.

Altogether, the identified errors in the paper call into question its level of peer-review. Normally, qualified reviewers would highlight potential issues with a study's methods and errors in the technical presentation of data would be caught and corrected. The number and type of errors in this paper, though, suggest insufficient time or attention was given to the peer-review process. This may be a bold accusation, but it is supported.

According to information and metrics available online, the Sunderland, et. al., manuscript was submitted to the Journal of Nuclear Medicine (JNM) on April 18, 2023. It underwent peer-review and was accepted without revision 8 days later on April 26. While it is not unheard of for papers to be accepted without revision, the review time of 8 days would likely surprise anyone with experience in scientific publishing.

I examined other research articles published by the JNM within the past six months. The average time between manuscript submission and acceptance was 142 days (N=106, 95% CI: 132-153 days). The likelihood that the referenced paper experienced JNM's normal review and revision process is low ($p = 0.0072$). An eight-day review time is even less than that of invited perspectives (M=60 days, N=19, 95% CI: 33-86 days), which are expected to undergo less critical scrutiny than research articles.

I found only one other article recently published by the JNM which appears to have had unusually accelerated peer-review (12 days): "Adverse Clinical Events at the Injection Site Are Exceedingly Rare After Reported Radiopharmaceutical Extravasation in Patients Undergoing 99mTc-MDP Whole-Body Bone Scintigraphy: A 12-Year Experience" by Parihar, et al. This study evaluated written radiology reports, rather than injection site images, to calculate and report an exceptionally low extravasation rate. The

study also reviewed medical records to assess harm, which are unlikely to accurately reflect incidence or causality.

For NRC's consideration, I think it is particularly noteworthy that the JNM is "self-published by the Society of Nuclear Medicine and Molecular Imaging (SNMMI)," which has publicly opposed characterizing and reporting extravasations. The papers by Parihar et. al., and Sunderland et. al., are the only two papers on the topic of extravasation published by the JNM over the last several years and the only two found to have undergone accelerated review. Additionally, on March 2, 2023, an SNMMI leader and member of numerous committees posted on the "SNMMI Connect" members' forum that the work by Sunderland et. al., "was fostered by the SNMMI". Selective acceleration of the peer-review process results in a diminished likelihood of objective scientific scrutiny and suggests the SNMMI may be unduly influencing JNM editorial staff to support their opposition to characterizing and reporting of extravasations.

Thank you,

Josh Knowland

Critique and Discussion of "Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose"

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The authors declare a potential conflict of interest and state it below

Josh Knowland is an employee of Lucerno Dynamics, LLC.

Author contribution statement

JK is the sole author of this work and is accountable for its content.

Keywords

Infiltration, Extravasation, Dosimetry, monte carlo, NRC, Nuclear Medicine

Contribution to the field

Radiopharmaceutical extravasation in nuclear medicine is an important topic that is being increasingly discussed in the literature. The Journal of Nuclear Medicine recently published a manuscript which reports on a study of 1000 oncologic PET patients and the rate of extravasation found. Unfortunately, the paper is rife with technical and methological errors. This paper provides a rebuttal and questions whether the author's conclusions can be accepted.

Critique and Discussion of "Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose"

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Keywords: infiltration; extravasation; dosimetry; Monte Carlo

1 Introduction

On May 25, 2023, the Journal of Nuclear Medicine (JNM) published an article ahead-of-print entitled "Multicenter Evaluation of Frequency and Impact of Activity Infiltration in PET Imaging, Including Microscale Modeling of Skin-Absorbed Dose" (1). The paper reports a retrospective study of 1,000 oncology patients from nine positron emission tomography (PET) imaging centers and several smaller clinics. The paper also describes a skin dose calculation using Monte Carlo simulations based on one patient image. For this case, the paper reports that absorbed dose to the skin was approximately 12 mGy.

The paper concludes that the "risk of significant tissue injury from diagnostic PET agents appears negligible, as is consistent with both clinical experience and the literature." It also asserts that a high level of quality exists in the administration of radiopharmaceuticals in PET practice.

There are, however, several problems with the work that raise questions about its conclusions. The methods are not well described, the results contain errors, and the peer-review process for this manuscript appears to have lacked rigor.

2 Methodology Problems

For its Monte Carlo simulations, the paper describes an assumed distribution of radioactivity within tissue and skin. However, the distribution is not representative of paravenous extravasation and minimizes the biological effects to muscle.

Extravasated radioactivity is modeled as being contained wholly within the dermis and subcutaneous fat. This assumption is based on previous work involving an injection of dyed saline into porcine subcutaneous fat—an experiment which explicitly excluded muscle. The paper also references "…tumescent fluid injections into the subcutaneous tissue for purposes of local anesthesia are common for several dermatologic procedures, including liposuction, cutaneous surgery, and drug administration." Subcutaneous administrations are very different than intravenous and are not an appropriate basis for model definition. Very low radiation doses to muscle are reported in Figures 3, 4,

and 5. These results are not explained, but because the underlying model for source activity distribution excludes activity within the muscle itself, absorbed dose may be grossly underestimated.

It is also unclear if the method of estimating initially extravasated radioactivity is appropriate. The paper describes "A measured activity of more than 370 kBq at the injection site, decay-corrected back to time of injection." This calculation seems to neglect biological clearance and instead corrects for physical decay only. An effective half-life of 30 minutes is mentioned in later discussions of dosimetry methods, however when estimating the initial activity, the paper makes no mention of biological clearance. Correction of physical decay alone would understate initial activity by nearly 300% for a typical pre-image uptake time of 65 minutes. Underestimation of initial activity would equally understate reported values for absorbed dose.

The results of the dosimetry method are not compared to existing, widely accepted models, and descriptions of the method lack details needed to replicate the work. Dimensions are provided for volumes of interest, but there is no definition of the material composition or densities used. Furthermore, the text indicates that the cross-sectional dimensions used for Monte Carlo simulation were 36 mm by 21 mm, but Figure 1 states 46 mm by 31 mm. It is not clear which dimensions were actually used for simulation, but absorbed dose for the smaller volume would be nearly double that of the larger.

The paper also states that a total of 1,000 oncology PET studies were analyzed from a variety of imaging centers. These studies were assumed to "…represent the variety of injection skills and injection techniques typically used in the clinical PET environment." The selection criteria for the imaging centers are not well described. Also, the paper does not provide a statistical justification for the sample size from each institution other than to say that data were from "consecutive patients who had the injection site in the field of view." The paper does not discuss details such as the number of technologists or their levels of experience.

Figures 2 and 3 also contain discrepancies or values that conflict with the text. In Figure 2, the x-axis of subpart A is identified as net activity in kBq. However, the figure's caption states units of MBq. In Figure 3, the y-axis is labeled as representing absorbed dose for an example extravasation of 0.83 MBq. The caption, however, references a 0.41 MBq case. Extravasated activities of 0.41 MBq and 0.83 MBq correspond to two different patients presented, but it is unclear which patient is described by Figure 3.

3 Discussion

The paper's conclusions seem to start with an assumption that diagnostic radiopharmaceutical extravasations are not a concern, and they should be challenged given the methodology problems identified. The paper states that, "Using the data and assumptions from this work, the risk of significant tissue injury from diagnostic PET agents appears negligible, as is consistent with both clinical experience and the literature."

The very low tissue doses reported reinforce the belief that injury is unlikely. However, these doses are understated because the model neglects self-dose to muscle and underestimates initially extravasated radioactivity. When an intravenous radiopharmaceutical is extravasated, it will not be confined within subdermal fat. The muscle tissue adjacent to the injection site is valid as both a source and target volume, but it is inappropriately ignored in the paper's dosimetry model. The paper did not provide evidence of validating its dosimetry model against existing published models.

Because the patient's skin is unlikely to be affected by activity near the extravasated vein, any effects to muscle tissue will likely be unnoticed and underdiagnosed by clinicians. Therefore, clinical experience and literature that has not appropriately evaluated underlying tissue injury should not be used to assert that injury from extravasation of diagnostic PET agents is negligible.

The paper also concludes that the rate of clinically meaningful extravasation (1% of injected activity) was between 0% and 0.37%. Inaccuracies in estimation of initially extravasated activity likely caused this rate to be understated. Considering the four cases of extravasation in Figure 2, proper application of biological clearance would cause all four to surpass the defined threshold. Four cases of meaningful extravasation (as opposed to the reported zero) would result in a rate of 0.4% with a 95% confidence interval of 0.11% to 1.02%. Even if the extravasation rate reported in this paper were accepted and applied to the 30 million radiopharmaceutical administrations every year in the US (from approximately 20 million nuclear medicine procedures), then up to 111,000 patients may experience clinically meaningful extravasations. Large extravasations have been shown to cause tissue absorbed doses of several Gray (3-6), diminished diagnostic image quality (7-9), and reduced quantitative accuracy (10-12).

The paper also states that "…our data indicate a high level of quality in the administration of radiopharmaceuticals in PET practice." It is important to note that the results apply only to those institutions, technologists, and PET procedures that were studied. The results from this paper only reflect what happened in these few centers during undefined observation periods and cannot be applied to the practice of nuclear medicine generally. For example, the paper has no description of the training and experience levels of participating technologists, and an unknown number of images with injection sites outside of the field of view were excluded from the study. Additionally, the paper estimates absorbed dose for a hypothetical "complete" extravasation of 470 MBq. It is unclear how this value was chosen, and it is not representative of the maximum injected activity for many nuclear medicine procedures in the US (2). Furthermore, this paper states that the study included no cases where intravenous access was through direct needle stick or butterfly catheter. However, many nuclear medicine centers do continue to use direct needle sticks and butterfly catheters for venous access.

Regarding large extravasations, the paper remarks that, "Instances have clearly been reported in the PET literature…and the field at large must be vigilant." This is an important point. Neither providers nor patients should worry about extravasations that involve insignificant radioactivity. However, for large extravasations, appropriate steps should be taken to characterize, minimize, and document the event. This paper used 1% of the injected activity as a threshold for clinical meaningfulness. However, tissue absorbed dose is a more appropriate metric for radiation protection of patients. The US Nuclear Regulatory Commission (NRC) has codified radiation exposure levels of concern in 10 CFR Part 35.3045 for medical patients if radioactive material is administered improperly or differently from that which was intended or prescribed. Those criteria include a radiation 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. For low LET radiation, 0.5 Sv is approximately the same as 0.5 Gy (500 mGy). NRC acknowledges that a radiation dose at or even above these levels may not necessarily result in physical harm to the patient, but rather instances of unintended dose to an organ or tissue may indicate a problem in the medical facility's practice or procedures. Routinely exceeding the 500 mGy threshold should act as an early indicator of increased risk.

Rigorous peer-review would typically address many of the shortcomings and errors identified in this paper. However, this paper seems to have been afforded an unusually accelerated peer-review process. The manuscript was submitted on April 18, 2023, underwent peer-review, and was accepted without revision 8 days later. Examination of other research articles published by the Journal of Nuclear Medicine (JNM) within the past six months reveals that the average time between manuscript submission and acceptance is 142 days (N = 106, 95% CI: 132-153 days). The likelihood that this paper experienced JNM's normal review and revision process is low (p = 0.0072). An eight-day review time is even less than the average for invited perspectives (M = 60 days, N = 19, 95% CI: 33-86 days), which are expected to undergo less critical scrutiny.

Only one other recently published JNM article was found to have had unusually accelerated peer-review (12 days): "Adverse Clinical Events at the Injection Site Are Exceedingly Rare After Reported Radiopharmaceutical Extravasation in Patients Undergoing 99mTc-MDP Whole-Body Bone Scintigraphy: A 12-Year Experience" by Parihar, et al. (13). This study evaluated written radiology reports, rather than injection site images, to calculate and report an exceptionally low extravasation rate. The study also reviewed medical records to assess harm, which are unlikely to accurately reflect incidence or causality. An absence of confirmation does not confirm an absence.

It is noteworthy that the JNM is "self-published by the Society of Nuclear Medicine and Molecular Imaging (SNMMI)." The SNMMI has publicly opposed characterizing and reporting extravasations using arguments that are not supported by science or clinical evidence. The papers by Parihar et. al., and Sunderland et. al., are the only two papers on the topic of extravasation published by the JNM over the last seven years and the only two found to have undergone accelerated review. Additionally, on March 2, 2023, an SNMMI leader and member of numerous committees posted on the "SNMMI Connect" members' forum that the work by Sunderland et. al., "was fostered by the SNMMI". The combination of undisclosed relationships and selective acceleration of the peer-review process results in a diminished likelihood of objective scientific scrutiny and suggests the SNMMI may be unduly influencing JNM editorial staff to support their public position on rulemaking.

4 Conflict of Interest

Josh Knowland is an employee of Lucerno Dynamics, LLC.

5 Author Contributions

JK is the sole author of this work and is accountable for its content.

6 Funding

None

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