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Reporting Nuclear Medicine Injection Extravasations as Medical Events

Comment On: NRC-2022-0218-0004
Reporting Nuclear Medicine Injection Extravasations as Medical Events

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General Comment

See attached file(s)

Attachments

NRC-2022-0218-Extravasations-MSKComments

Memorial Sloan Kettering Cancer Center

September 1, 2023

Submitted via Regulations.gov

Secretary Brooke P. Clark
United States Nuclear Regulatory Commission (NRC)
Washington, DC 20555-0111
Attn.: Rulemakings and Adjudications Staff

Docket ID: NRC-2022-0218

Dear Sir/Madam:

The Medical Health Physics Department of Memorial Sloan Kettering Cancer Center (MSK) thanks the Nuclear Regulatory Commission (NRC) for the opportunity to submit feedback on the proposed rule and language for the reporting of nuclear medicine injection extravasations as medical events [NRC-2022-0218; RIN 3150-AK91] (proposed rule).

General Comments:

Extravasation of injected radiopharmaceuticals can potentially impact the clinical information content and quantitative accuracy of diagnostic studies and the effectiveness and/or toxicity of therapeutic procedures. Nuclear Medicine providers have been and are aware of these possible consequences of extravasated radiopharmaceuticals and have long been accustomed to recognizing and dealing with them without any regulatory intervention. For example, virtually all patients injected with diagnostic radiopharmaceuticals are routinely imaged and thus any significant extravasations are already sensitively and unambiguously identified. **Extravasation of radiopharmaceuticals is thus clearly a practice-of-medicine issue and is and should remain outside the scope of regulatory oversight.** Regulatory intrusion into Nuclear Medicine practice by now classifying extravasations as "medical events" is therefore not only inappropriate and unnecessary but would introduce burdensome reporting requirements on already resource-challenged clinical facilities.

Extravasations of radiopharmaceuticals is remarkably infrequent. There are ~20 million doses of radiopharmaceuticals administered intravenously each year in the United States.[1] In a

[1] National Research Council (US) and Institute of Medicine (US) Committee on State of the Science of Nuclear Medicine. Advancing Nuclear Medicine Through Innovation. Washington (DC): National Academies Press (US) (2007) 2, Nuclear Medicine. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11471/; *see* Delbeke, D., & Segall, G.M. (2011). Status of and Trends in Nuclear Medicine in the United States. *J Nucl Med.* 52, 24S–28S; *see also* Mettler, F. A., Faulkner, K., Gilley, D. B., *et al.* (2009). Radiologic and Nuclear Medicine Studies in the United

recent meta-analysis, van der Pol *et al.* summarized 37 previously published reports of the consequences of radiopharmaceutical extravasation.[2] Of a total of 3016 diagnostic radiopharmaceutical extravasations, only three (< 0.1%) were associated with adverse reactions. In each case the adverse reaction was limited to the skin adjacent to the injection site. Importantly, no adverse reactions were reported for the more than 3000 cases of extravasation of such commonly used agents as ^{99m}Tc-, ^{123}I-, ^{18}F-, and ^{68}Ga-labelled radiopharmaceuticals. There are **no clinical data**, therefore, that **indicate that extravasation of diagnostic radiopharmaceuticals is actually a patient-safety issue**.

Because of the complex dosimetry of extravasated radiopharmaceuticals, risk-based regulations are not logically adaptable to such extravasations and therefore scientifically reasonable regulatory oversight of extravasation events is not practical. In a recent analysis of 1,000 PET/CT patient studies from 10 facilities (1), 460 of 1,000 patients had activity at the injection site was clearly visualized. However, only 6 of 1,000 patients had activity at the injection site in excess of 370 kBq (10 µCi), with no activities greater than 1.7 MBq (45 µCi). However, quantitative assessment of activities averaged only 34 kBq (0.9 µCi), corresponding to only 0.008% of the injected activity. Monte Carlo simulation-based absorbed dose calculations for the extrapolated 470-MBq infiltration resulted in a hypothetical absorbed dose to the epidermis of less than 1 Gy, a factor of 2 lower than what is required for even minimal deterministic skin reactions. Analysis of the dose distribution demonstrates that the dermis acts as a β-shield for the radiation-sensitive epidermis. Dermal shielding is highly effective for low-energy ^{18}F positrons although less so with the higher-energy positrons of ^{68}Ga. Shallow doses to the epidermis from infiltration events are thus likely substantially lower than previously reported because of absorption of β-particles in the dermis.

Specific Comments to Requested Areas for Feedback:

I. Definitions:

1. What term should the NRC use (e.g., extravasation, infiltration) when describing the leakage of radiopharmaceuticals from a blood vessel or artery into the surrounding tissue?

> The term "leakage" implies a passive process as opposed to something caused by injection itself and should be reconsidered.
>
> A technical definition for this phenomenon will need to be established. If radioactive material is injected, there will always be a larger concentration at the site due to the natural adherence and porosity of the blood vessels. In the absence of clear criteria, every radiopharmaceutical injection may qualify.

States and Worldwide: Frequency, Radiation Dose, and Comparison with Other Radiation Sources – 1950-2007." *Radiology. 253*(2), 520-531.

[2] van der Pol J., Vöö S, Bucerius J., & Mottaghy F.M. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. (2017). *Eur. J Nucl Med Mol Imaging*. 44(7), 1234-1243.

2. What criteria should the NRC use to define "suspected radiation injury"?

As a start, the NRC should survey the peer reviewed literature to compile evidence-based guidance relating radionuclide-specific activities to deterministic radiogenic health effects in the absence of any findings from this review, the scope of the rule making process should be revaluated.

If the NRC chooses to proceed, it should use existing standards such as the NCI's Common Terminology Criteria for Adverse Events (CTCAE) that would facilitate compliance.[3] Furthermore, a "suspected radiation injury" should exclude injuries classified as CTCAE Grade 1 and Grade 2 events to avoid the excess reporting of clinically insignificant events and or misattributed ones.

Additionally, the term should be defined further and specify *who* makes the determination of a suspected radiation injury otherwise anyone could self-diagnose. For example, '*...an observable deterministic health effect of medical significance to the area around an injection site that can be reasonably attributed to radiation through specific observations of an AU or physician*.'

3. What techniques or methods should be included in the definition of "medical attention"?

In addition to the techniques used to reduce the chance, severity, or symptoms of a suspected radiation injury, "medical attention" must rise to a certain threshold beyond alleviative care related to an injection and require the input of a clinician and a note that is documented in the patient's medical record indicating the care provided.

II. Procedures:

4. What steps could the licensee take to minimize the chance of a radiopharmaceutical extravasation occurring?

This question pertains to the practice of medicine and should not be considered.

5. What steps should the licensee take when an extravasation is suspected or discovered?

This question pertains to the practice of medicine and should not be considered.

6. What techniques, technologies, or procedures (e.g., post-treatment imaging, visual observation, patient feedback) should be used to help identify an extravasation during or immediately after a radiopharmaceutical injection?

This question pertains to the practice of medicine and should not be considered.

7. What techniques, technologies, or procedures (e.g., post-treatment imaging, survey measurement) should be used to better characterize an extravasation after radiopharmaceutical treatment?

This question pertains to the practice of medicine and should not be considered.

[3] National Institutes of Health-National Cancer Institute. Quick Reference: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. November 17, 2017

8. What information should licensees provide to nuclear medicine patients on how to identify an extravasation and how to follow up with their physician if they suspect a radiation injury?

This question pertains to the practice of medicine and should not be considered.

9. When should a reportable extravasation be counted as "discovered" for the purposes of notification (e.g., when medical attention is administered, when the physician identifies that the injury is from radiation)?

An extravasation under the proposed rule should be counted as "discovered" only upon observation from an AU or physician that there is an observable deterministic health effect of medical significance to the area around an injection site that can be reasonably attributed to radiation.

11. Who (e.g., patient's primary physician, authorized user, nuclear medicine technician) should be able to identify an extravasation that could result in a "suspected radiation injury"?

Licensees have policies in place about the identification and/or discovery of extravasations.

III. Healthcare Inequities:

13. What regulatory actions could help ensure that extravasations in patients affected by healthcare inequities are accurately assessed and reported?

Any regulations regarding the reporting of extravasations as medical events or regulatory guidance to assist with the compliance of the preliminary proposed rule must be accessible to all facilities, especially smaller ones, to advance patient safety while not creating a new, potentially significant, regulatory burden that may impact the availability and or cost of care.

Respectfully submitted,

The MSK Medical Health Physics Department