LUCERNO DYNAMICS, LLC
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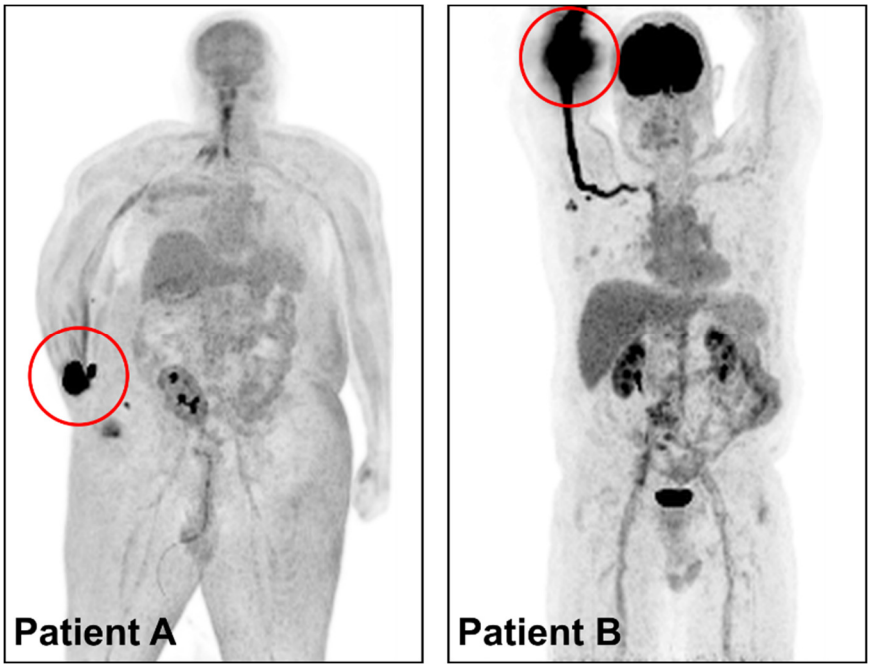
September 8, 2022

Christopher Hanson, Chairman
Jeff Baran, Commissioner
David Wright, Commissioner
Annie Caputo, Commissioner
Bradley Crowell, Commissioner
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Subject: Additional Evidence Regarding Radiopharmaceutical Extravasations

Dear Chairman Hanson, Commissioner Wright, Commission Baran, Commissioner Caputo, and Commissioner Crowell,

I am writing to update you on two recent examples of nuclear medicine radiopharmaceutical extravasation which I feel demonstrate the importance of event characterization and dosimetry. The following two images show maximum intensity projection (MIP) views of the diagnostic PET/CT scans performed for two patients, which I will refer to as Patient A and Patient B. For each, the extravasated radiopharmaceutical is circled in red.



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Visually, both cases indicate an extravasation near the injection site. The extravasation of Patient A appears smaller than that of Patient B, but organ uptake is also less well defined. Radioactive lymphatic drainage is visible in the scan for Patient B indicating ongoing biological clearance of the extravasate.

The radiopharmaceutical injections of both these patients were monitored in real-time using high sample-rate nuclear uptake probes. Active monitoring provided an advance indication to the clinicians of possible residual injection site radioactivity, so they included the injection site in the imaging field of view. Monitoring also provided dynamic data for full determination of the effective half-life of extravasated activity.

These extravasation cases were characterized using the methods and tools I wrote to you about on July 20, 2022 (Subject: Advancements in Dosimetry for Radiopharmaceutical Extravasations). Each case took less than five minutes of work. As you know, those characterization and dosimetry tools have been released publicly at no cost, and they can be used to quickly analyze cases of radiopharmaceutical extravasation for absorbed dose to patient tissue. For your perusal, I have attached the summary reports generated for these two patients but will also go into some detail about the analysis.

For Patient A, 0.11 mCi of 18F-FDG was residual to the injection site at the time of PET imaging, and the dynamic injection monitoring data indicated that the effective half-life of this extravasated radioactivity was 27.5 minutes. For Patient A, absorbed dose to 5 cm3 of arm tissue was calculated to be **0.48 Gy**. Based on the absorbed dose, the monitoring information, and the amount of residual activity at the injection site, no further action was needed or taken with this case.

For Patient B, 2.93 mCi of 18F-FDG was still within tissue at the injection site at time of imaging and the effective half-life was 32.4 minutes. In fact, the residual radioactivity present and the effective half-life together indicate that Patient B suffered a complete extravasation with all 11.77 mCi being initially injected into the arm tissue. The absorbed dose to 5 cm3 of tissue was calculated to be **11.24 Gy**. Based on these results, the clinical providers for Patient B are adding them to a registry for long-term follow-up.

Using qualitative visual assessment of these two cases, it would be impossible to determine the true significance and severity of each event. But, by monitoring the residual radioactivity and performing characterization, the differences become clear. Extravasated radioactivity is clearly visible in the scan for Patient A, but in fact the tissue absorbed dose was calculated to be below the existing medical event reporting threshold. On the other hand, by using simple uptake probes and free characterization tools, we learned that the extravasation of Patient B **would qualify as not only a medical event, but also an Abnormal Occurrence** if not for the policy to exempt extravasations from all reporting and notification.

In addition to the implications of high absorbed doses to healthy tissue, large extravasations can negatively impact the uptake processes that PET and SPECT scanning depend on, and in turn, negatively impact the diagnostic quality of the images. Based on the characterization results of

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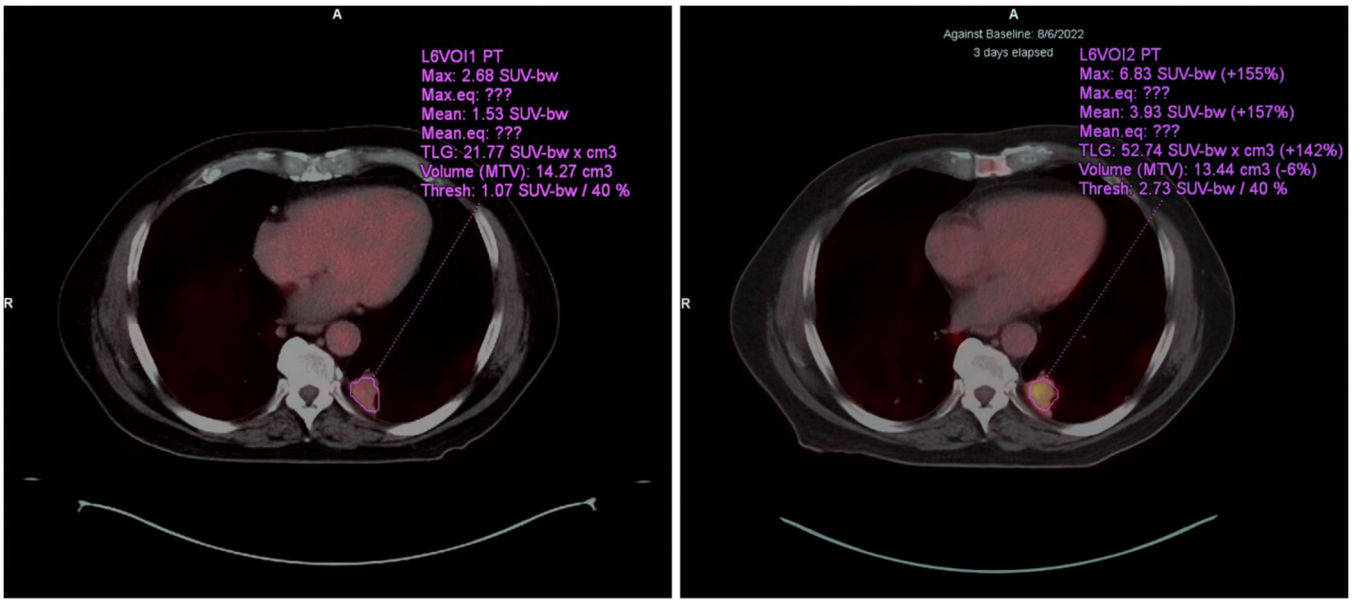
Patient B, clinical staff decided to repeat the PET imaging three days later. The following images show the difference in PET/CT quantification caused by the extravasation.




**Patient B, Baseline PET/CT Scan** **Patient B, Repeated PET/CT Scan**

In this case, the extravasation caused a significant understatement of three quantitative measures that characterize the activity of the target tumor:

| | Extravasated PET/CT Scan | Repeated PET/CT Scan | % Error Due to Extravasation |
|---|---|---|---|
| SUVmax | 2.68 | 6.83 | - 61% |
| SUVmean | 1.53 | 3.93 | - 61% |
| Total Lesion Glycolysis (TLG) | 21.77 | 52.74 | - 59 % |
| Metabolic Tumor Volume (MTV) | 14.27 | 13.44 | 6 % |

These quantitative measurements are used to help assess treatment. Using the extravasated images could result in incorrect treatment assessments.

These two cases show that is easy to characterize extravasations for both regulatory reporting and patient care. Arguments suggesting characterization is difficult, time-consuming, and costly are incorrect and intended to dissuade NRC from correctly addressing extravasations as medical events.

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Sincerely,

Josh Knowland

Cc: Amy Powell
Bernice Ammon
Carol Lazar
David Brown
Diana Diaz-Toro
Janet Lepre
Kevin Williams
Lisa Dimmick
Marian Zobler
Marilyn Diaz Maldonado
Molly Marsh
Matt Dennis
Ron Lattanze

Attachments:

1. Patient A Summary.pdf
2. Patient B Summary.pdf

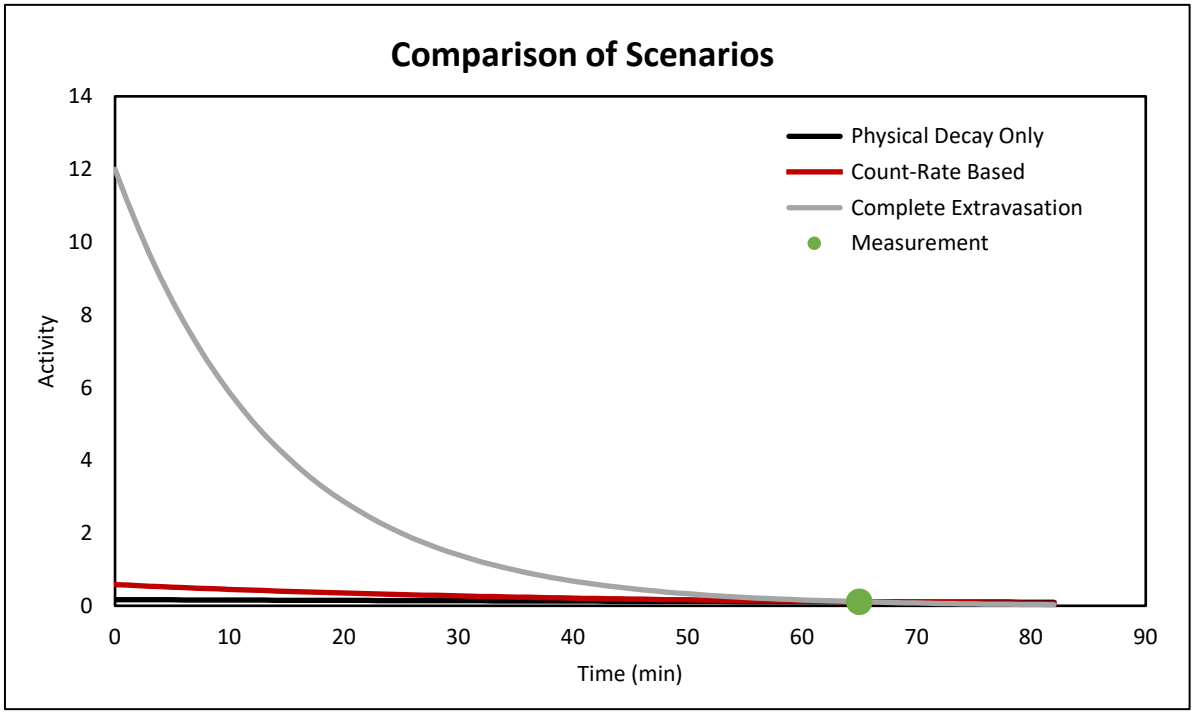
**RIDE**
Radiopharmaceutical Infiltration Dosimetry Estimation

| | |
|---|---|
| **Record Number** | PATIENT A |
| **Analysis Performed By** | JK |
| **Analysis Date** | 8/29/2022 |

| | | |
|---|---|---|
| **Isotope** | F-18 | |
| **Injected Activity** | 12.00 | mCi |
| **Measured Activity** | 0.11 | mCi |
| **Measurement Time Post-Injection** | 65.0 | min |

## Injection Site Tissue Absorbed Dose Scenarios

| Scenario | Initial Activity (mCi) | Effective Half-life (min) | Absorbed Dose to 5g of Tissue (Gy) |
|---|---|---|---|
| Physical Decay | 0.17 | 109.8 | 0.56 |
| Count-Rate | 0.59 | 27.5 | 0.48 |
| Complete | 12.00 | 9.7 | 3.43 |



**RIDE**
Radiopharmaceutical Infiltration Dosimetry Estimation

| | |
|---|---|
| **Record Number** | PATIENT B |
| **Analysis Performed By** | JK |
| **Analysis Date** | 8/29/2022 |

| | | |
|---|---|---|
| **Isotope** | F-18 | |
| **Injected Activity** | 11.77 | mCi |
| **Measured Activity** | 2.93 | mCi |
| **Measurement Time Post-Injection** | 65.0 | min |

## Injection Site Tissue Absorbed Dose Scenarios

| Scenario | Initial Activity (mCi) | Effective Half-life (min) | Absorbed Dose to 5g of Tissue (Gy) |
|---|---|---|---|
| Physical Decay | 4.41 | 109.8 | 14.29 |
| Count-Rate | 11.77 | 32.4 | 11.24 |
| Complete | 11.77 | 32.4 | 11.24 |