Novel Method to Calculate Equivalent Dose to Tissue in Cases of Radiopharmaceutical Extravasation

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Background

Radiopharmaceutical extravasation can result in high concentrations of activity remaining within tissue near the injection site resulting in significant dose over time (2-9).

An existing published technique for extravasation dosimetry assumes the entire injection is extravasated into tissue with a minimal volume (7). This technique assumes no movement or reabsorption of the activity over time—it decays entirely in situ.

A second technique improves upon the first by assuming the biological clearance of the radiopharmaceutical. The body will clear the radiopharmaceutical in the interstitial space through venous and lymphatic capillaries at a rate dependent on the concentration gradient between interstitial fluid and blood as well as the degree of vascularization in the local area. The clearance process typically assumes a half-time of 2 hours, but can be up to 8 or 10 hours based on vascularization (10). This assumption has been broadly confirmed by studies that intentionally extravasate saline and then monitoring the rate of clearance over time (11-15). Assumed clearance rate can improve dose estimation accuracy, but the technique still assumes complete extravasation within an unchanging volume.

A third technique assumes radioactive decay and uses static nuclear images to measure extravasation volume and activity at imaging time. It still assumes an unchanging volume and no biological clearance.

These techniques result in a flawed estimate of a patient's tissue dose. To improve dose accuracy for a particular patient, information is needed about the changes in extravasation activity and volume over time, which static imaging cannot provide (7,13-15). Serial images of the injection site or continuous measurement with a scintillation counter or radiation monitor have been proposed to estimate the rate of biological clearance (3,5,8,10,16-18).

In this work, we sought to develop a more accurate technique of injection site tissue dosimetry for cases of extravasated radiopharmaceuticals that would account for both biological clearance and volume expansion over time.

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Methods

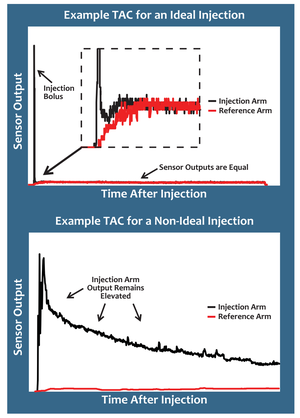
Estimation of the rate of biological clearance was made using topical injection site sensors (Lara®, Lucerno Dynamics). The sensors provide a measurement once per second and the change in their output is representative of changes in local activity (19).

The time-activity curve (TAC) produced by Lara for ideal intravenous injections shows an initial bolus spike from the injection-arm sensor followed by an immediate reduction to a level consistent with that measured by the reference-arm sensor. This indicates that the injected radiopharmaceutical is systemic with low probability of residual injection site activity.

An extravasation that leaves significant activity near the injection site results in an elevated TAC. During reabsorption, sensor output will decrease accordingly. Sensor output and the presence of residual activity near the injection site has been clinically validated using dynamic imaging (20).

The figure to the right shows examples of TACs from both ideal and non-ideal injections.

With the availability of TAC data for the injection site, one can improve upon the existing extravasation dosimetry techniques.



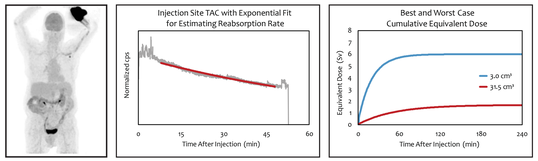
Overall, the steps in our novel technique are:

1. Calculate the activity clearance rate using injection site TAC data with a least-squares fit of an exponential function.
2. Determine the imaging-time extravasation activity and volume using static images.
3. Extrapolate backwards to injection time using imaging time activity and the clearance rate to find initial extravasation activity.
4. Define minimal and maximal initial extravasation tissue volumes using injected radiopharmaceutical and saline volumes. Minimal volume is calculated as twice the injected radiopharmaceutical volume while maximal volume includes the entire volume of saline flush. We used 1cm^3 if calculated volume was less than 1cm^3.
5. Determine the activity within the initial extravasation tissue volumes at imaging time using nuclear medicine image data centered about the maximal voxel.
6. Calculate the activity over time within the initial extravasation volumes by fitting an exponential function to the initial- and imaging-time activities.
7. Calculate the dose per unit time for the initial extravasation tissue volumes based on published data for spherical volumes of muscle.
8. Integrate over four physical half-lives to find total dose to the initial extravasation volumes.

Note: Dose is only calculated for the initial extravasation tissue volume because this tissue would be exposed to the highest concentration of activity for the longest period of time. This limits assumptions and simplifies calculations, but does result in an underestimation of the true total tissue dose.

Results

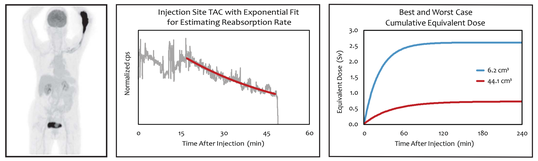
Below are the dosimetry results for three clinical cases of diagnostic radiotracer extravasation using the proposed technique.



Case #14547. A staging PET/CT study was ordered to assess a tumor in the pancreatic head that was felt to be unresectable due to neurovascular involvement. The patient was injected in the left forearm with 10.2 mCi of 18F-FDG and the Lara system identified the likely presence of residual activity near the injection site. The nuclear medicine physician ordered a repeat PET scan the next day.

Comparison of extravasated and non-extravasated axial images of the pancreatic tumor revealed that the extravasation caused SUV to be understated by 65%.

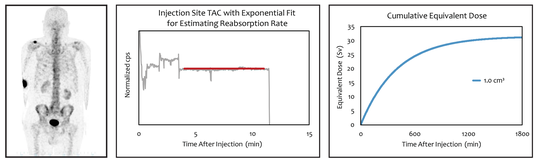
- **Radiotracer Activity:** 10.2 mCi
- **Radiotracer Volume:** 1.5 mL
- **Saline Flush Volume:** 30.0 mL
- **Time Before Imaging:** 62 min
- **Initial Tissue Volumes:** 31.5 and 3.0 cm^3
- **Biological Clearance Half-Life:** 57.4 min
- **Image-Time Activity:** 5.19 mCi
- **Dose Rate:** 3.1 and 28.4 mSv/mCi-min
- **Total Equivalent Dose:** 1,700 to 6,000 mSv



Case #15170. As part of a metastatic disease assessment study, the patient was injected in the left antecubital with 9.99 mCi of 18F-FDG using an auto-injector. The Lara system indicated the likely presence of excess radiotracer near the injection site even though the auto-injector reported an error-free injection.

The imaging study was repeated three days later and revealed the extravasation caused an understatement of SUV by 73%.

- **Radiotracer Activity:** 9.99 mCi
- **Radiotracer Volume:** 4.0 mL
- **Saline Flush Volume:** 41.0 mL
- **Time Before Imaging:** 62 min
- **Initial Tissue Volumes:** 44.1 and 6.2 cm^3
- **Biological Clearance Half-Life:** 27.6 min
- **Image-Time Activity:** 1.62 mCi
- **Dose Rate:** 2.2 and 14.4 mSv/mCi-min
- **Total Equivalent Dose:** 700 to 2,600 mSv



Case #16380. The patient was injected in the right antecubital with 26.2 mCi of Tc99m-MDP. The Lara system identified the likely presence of excess radiotracer near the injection site and time-activity curve data indicated no biological clearance. The interpreting radiologist estimated the extravasation to be at least 50% and found the SPECT images to be of no diagnostic value.

No quantification could be made from the SPECT images and the extravasated tissue was partially outside of the imaging field of view. The visible portion of the extravasation at imaging time was measured to be 9.17 cm^3, but we estimated its true volume to be 30 cm^3.

- **Radiotracer Activity:** 26.2 mCi
- **Radiotracer Volume:** 0.5 mL
- **Saline Flush Volume:** 0.0 mL
- **Time Before Imaging:** 201 min
- **Initial Tissue Volumes:** 1.0 cm^3
- **Biological Clearance Half-Life:** ∞
- **Image-Time Activity:** 8.9 mCi
- **Dose Rate:** 5.95 mSv/mCi-min
- **Total Equivalent Dose:** 31,300 mSv

Conclusions

We have described and demonstrated a novel technique for calculating equivalent dose to tissue in the case of radiopharmaceutical extravasation.

The technique differs from existing techniques by accounting for the ways in which both the extravasation activity and volume change over time. Inclusion of this dynamic information may result in more accurate estimation of equivalent dose to the initially extravasated tissue volume.

The table below compares our novel technique's results to existing techniques.

	Equivalent Dose to Extravasated Tissue (mSv)			
Case ID	Technique 1	Technique 2	Technique 3	Novel Technique
14547	3,300 - 70,100	2,600 - 24,200	600	1,700 - 6,000
15170	2,300 - 25,700	1,800 - 9,300	400	700 - 2,600
16380	141,400	20,300	1,500	31,300

- ***Technique 1*** *assumes that the entire injection is extravasated into a volume of tissue equal to its injection volume. Furthermore, it assumes no reabsorption and no movement of the radiopharmaceutical. Dose was calculated with and without saline flush.*
- ***Technique 2*** *assumes a biological clearance half-time of 120 minutes and 100% extravasation into a volume equal to twice the injected radiopharmaceutical volume or the injected radiopharmaceutical volume plus the saline flush volume.*
- ***Technique 3*** *uses activity and volume from static images and accounts for physical decay, but assumes no biological clearance.*

Nuclear medicine practitioners may reject technique 1 as implausible because the assumption of 100% extravasation with no biological clearance is easily refuted by static images. If all activity decays near the injection site, no image could be constructed.

Neither technique 2 nor 3 accurately account for changes over time. Technique 2 assumes biological clearance with a half-time of 120 minutes, however, the example cases presented here show that 18F-FDG can clear faster than that. An assumed clearance half-time of 120 minutes would over-estimate the tissue dose in these examples. In the Tc99m-MDP case, biological clearance was essentially non-existent, so an assumed clearance rate would underestimate the dose.

Tissue dose is dependent on not only the radiopharmaceutical radiation type and energy, but also how it is administered and how it clears. For example, Tc99m-MDP extravasations may lead to higher than anticipated tissue dose. First, many Tc99m-MDP procedures are performed as a "straight stick" with no saline flush - leading to very small initial volumes with high specific activity. Secondly, the molecular charge of MDP limits the rate at which it is transported across cell membranes and thus the biological clearance rate. Finally, these procedures use relatively higher injected activity than other procedures, and Tc99m has a significantly longer physical half-life than other diagnostic radiotracers.

Along with the impact that extravasations can have on diagnosis and subsequent treatment (21), there is evidence that the radiation dose to injection site tissue can cause both deterministic (1-2,4,6,8,16-17) and stochastic (22) harm.

We propose that patient care teams should be aware of and prepared for the possibility of extravasation when using radiopharmaceuticals. Furthermore, they should monitor each procedure for extravasation and perform injection site dosimetry. We have demonstrated a method of dosimetry that may be more accurate than existing methods due to inclusion of dynamic time-activity data.

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