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January 10, 2020

Michael Layton, Director
Division of Materials, Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards
Nuclear Regulatory Commission

Dear Michael,

As requested by Dr. Said Daibes, Lucerno is providing NRC with the abstract, a copy of the American College of Nuclear Medicine acceptance letter, and the poster that will be presented at the Society of Nuclear Medicine and Molecular Imaging and American College of Nuclear Medicine Mid-Winter meeting in two weeks.

Please note that the novel dosimetry method described in this poster is being submitted for publication in a medical physics journal at the request of the journal's editor. Lucerno will forward more information about the publication of this method once we hear from the journal.

We request that the contents of the poster not be shared outside of the NRC staff until after January 24, 2020. Thank you for your consideration of this request. As promised in our December communication, Lucerno will be forwarding you some additional patient extravasation dosimetry results later this month.

I am sorry that we were not able to meet while I was in Washington DC earlier this week. I will be returning on February 5, 2020 and if you are available, I would appreciate the opportunity to stop in and introduce myself.

Sincerely,

DocuSigned by:
Ron Lattanze
0C2FCDBE78A7435...

Ron Lattanze
Chief Executive Officer

Enclosures:
1. Submitted Abstract
2. Acceptance Notice
3. Poster

cc:
Chris Einberg
Lisa Dimmick
Said Daibes
Kellee Jamerson
Donna-Beth Howe

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

Josh Knowland, Jackson W. Kiser

Objectives:

Radiopharmaceutical extravasations can result in high concentrations of activity remaining within tissue near the injection site. This activity can expose the tissue to significant dose over time. Existing dosimetry methods do not accurately account for changes in extravasated activity or its volume over time. While it may be impractical to dynamically monitor changes in extravasated activity using a PET/CT or gamma camera, radiation detectors may be a practical alternative.
The Lara® System (Lucerno Dynamics, Cary, NC) consists of scintillation detectors for monitoring radiopharmaceutical injection quality. The system records decay-corrected time-activity curves (TACs) of the activity near the injection site. The objective of this work was to develop a new method of extravasation dosimetry that considers the radiopharmaceutical reabsorption rate as measured by topical scintillation detectors.

Methods:

Extravasation activity is quantified using static PET/CT images with a threshold of 10% of SUV_{MAX}. An exponential function is fit to decay-corrected TAC data using a least squares method. The decay constant for the exponential function is used as an estimate of reabsorption rate. This rate is used to estimate the initial extravasation activity by extrapolating the measured activity in the static images back to the time of injection. Initial extravasation tissue volume is estimated with two approaches: twice the injected radiopharmaceutical volume and the injected radiopharmaceutical volume plus the saline flush volume. Dose rates are calculated using IDACdose 2.1 software using spherical volumes of muscle tissue. Equivalent dose to the tissue is then calculated by multiplying dose rate with activity over time and integrating.

Results:

The method was used to calculate equivalent tissue dose for 2 cases of clinical extravasation of 18F-FDG and the results were compared to three existing methods of extravasation dosimetry. Injection site activities at the time of imaging were 1.6 mCi and 5.2 mCi. Estimated half-time reabsorption rates were 27.6 min and 55.9 min. Initial volumes ranged from 3.0 cm^3 to 44.1 cm^3. Dose rates ranged from 2.2 mSv/mCi-min to 28.5 mSv/mCi-min. Equivalent dose calculations fell within the range of other methods, but with a tighter spread of estimates The new method resulted in equivalent dose estimates of 0.7 Sv to 6.0 Sv (0.7-6.0 Gy) whereas existing methods estimated 0.9 Sv to 70.1 Sv (0.9 Gy to 70.1 Gy).

Conclusions:

A new method of dosimetry for diagnostic radiopharmaceutical extravasation was developed and tested. The method improved upon existing methods by incorporating measurements of activity near the injection site over time. The method demonstrates that tissue near the injection site can be exposed to significant equivalent dose in cases of extravasation.

December 4, 2019
Dear Dr. Kiser
On behalf of the American College of Nuclear Medicine, I am pleased to inform you that your abstract, Control ID: 47 (now poster 13) Novel Method to Calculate Equivalent Dose to Tissue in Cases of Radiopharmaceutical Extravasation has been accepted for poster presentation at the ACNM Annual Meeting. Poster **must** be mounted, by **Thursday, January 23rd at 3:00pm (local time)** and can be removed **anytime between Noon and 6pm** on Saturday, January 25, 2020.
Poster board specifications are as follows: 6 feet wide & 4 feet tall.
Presentation Date: Friday, January 24, 2020
Presentation Time: 12:15-1:15 pm (local time)
The meeting will be held at the **Tampa Marriott Water Street, Tampa, FL** on January 23-25, 2020. The Ursula Mary Kocemba-Slosky, Ph.D. award, the ACNM best abstract award; along with the Young Investigators Awards, comprised of three $500 essay awards and two $750 travel grant awards, will be awarded during the ACNM new fellows induction ceremony and Awards Banquet on **Friday night, January 24, 2020 @ 7pm**. *Tickets are sold separately and may be purchased at the registration desk based on availability ($150/person, Residents: $60/person).*
In addition, you will be able to submit your full manuscript for publication consideration no later than April 20, 2020. The Clinical Nuclear Medicine Journal editorial board will assist in an ***expedited*** *review the manuscripts and, if accepted, chosen manuscripts will be published in the Clinical Nuclear Medicine Journal - ACNM's official publication.* Authors of ACNM presentations may send their full manuscript to Clinical Nuclear Medicine through the on-line "Editorial Manager" manuscript management system http://www.editorialmanager.com/cnm/. Please also forward a copy of your manuscript to Delicia Hurdle in the ACNM office at dhurdle@snmmi.org no later than ***April 20, 2020***.
To take advantage of the early-bird rates, please register by December 12. The link to the registration site can be found here: MWM 2020 Registration. After December 12th, please visit the ACNM Annual Meeting website to register for the meeting and for information to make your hotel and travel reservations.
ePoster Information: Instructions on uploading your ePoster wil be provided, on or about Friday, December 20, 2019. We would like to have as many posters available for viewing no later than Friday, Janurary 17, 2020.
If you have questions regarding this correspondence, please contact Delicia Hurdle, Senior Program Manager at dhurdle@snmmi.org or 703-667-5121.
Thank you for your contribution to the ACNM Annual Meeting. We look forward to seeing you in Tampa!
Sincerely,

Erin Grady, MD
Simin Dadparvar, M.D.

Erin Grady, MD, FACNM
ACNM President ACNM

FACNM Simin Dadparvar, MD
Scientific Abstract Committee

Feedback

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

Josh Knowland, Lucerno Dynamics LLC, Cary NC and Jackson W. Kiser M.D., Carilion Clinic, Roanoke VA

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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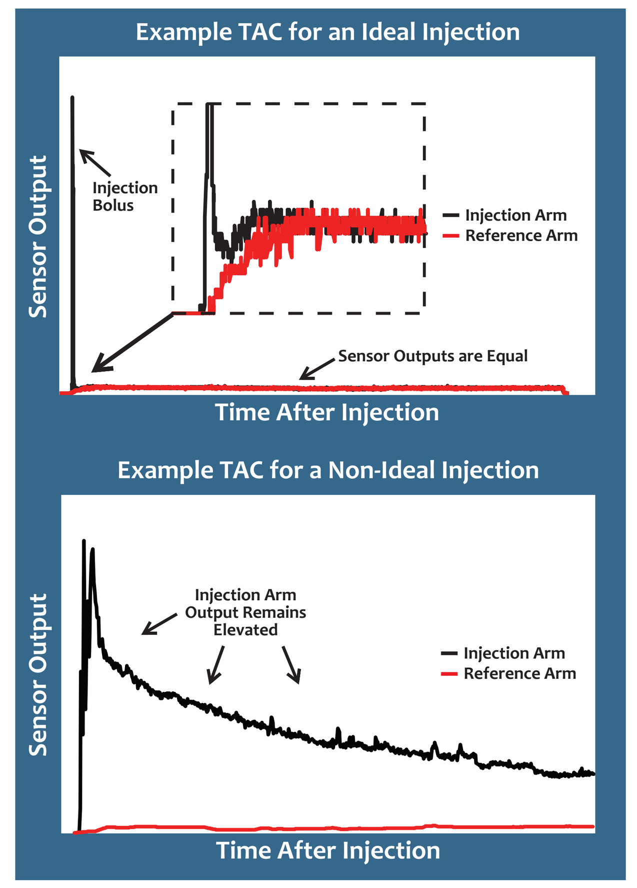
Methods

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.

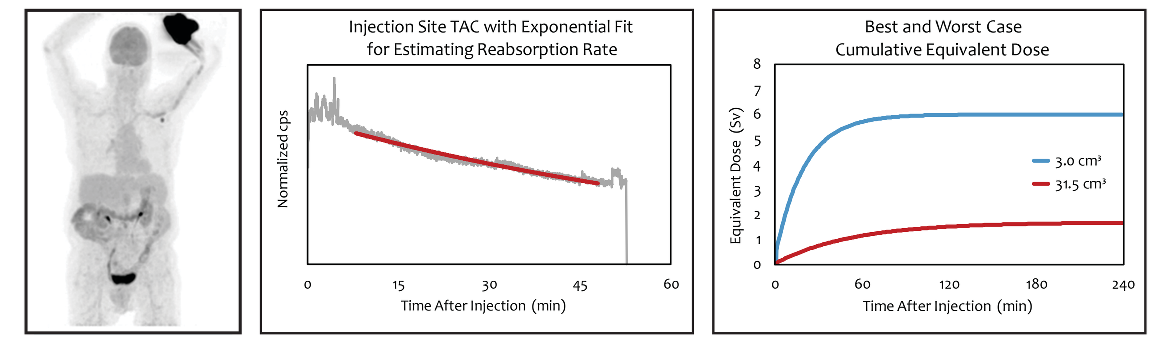
Overall, the steps in our novel technique are:

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 $1 cm^3$ if calculated volume was less than $1 cm^3$.
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

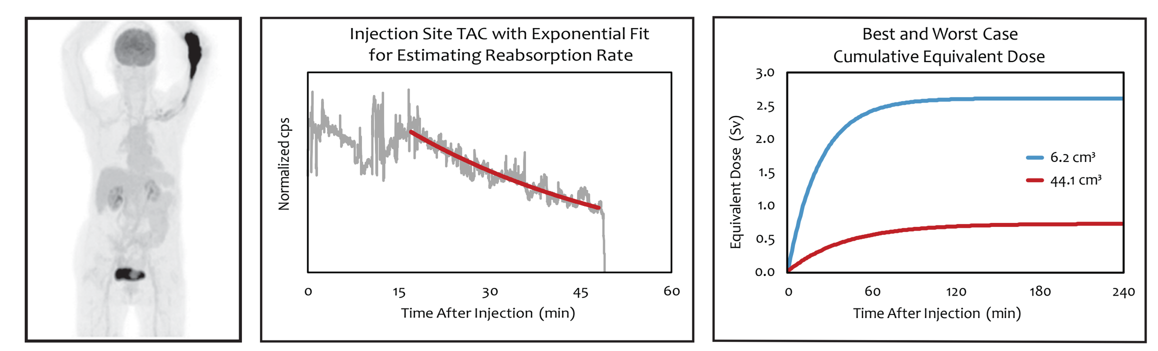
Below are the dosimetry results for three clinical cases of diagnostic radiotracer extravasation using the proposed technique.



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%.

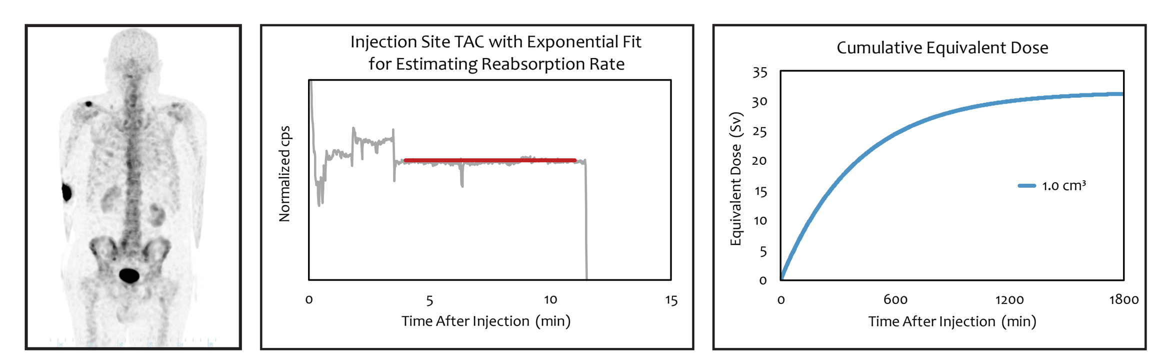
- **Radiotracer Activity: 10.2 mCi**
- **Radiotracer Volume: 1.5 mL**
- **Saline Flush Volume: 30.0 mL**
- **Time Before Imaging: 62 min**
- **Initial Tissue Volumes: 31.5 and 3.0 cm^3**
- **Biological Clearance Half-Life: 57.4 min**
- **Image-Time Activity: 5.19 mCi**
- **Dose Rate: 3.1 and 28.4 mSv/mCi-min**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