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December 20, 2019

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 the Lucerno team drafted our medical physics journal submission of our dosimetric calculation method, we added supporting evidence using Monte Carlo simulations. Over the past several weeks we have completed this simulation development. We then ran simulations from three previously submitted cases to the NRC. The method and results of these simulations are attached for your team's review. In summary, the simulations confirm the dosimetric method that we have used to calculate the tissue dose for patients who experience significant or moderate extravasations.

Due to this simulation work, we have only processed three new patient cases (attached for your team's review). Since the holidays are upon us, we decided to send these three cases to you now. We will work on the next seven when we return from the holiday break.

I will be in Washington DC for several meetings on January 7, 8, and 9. Please let me know if you would like to meet. I'd be happy to stop by the office to get your perspective on our October 9 request.

Wishing you and your team a relaxing and healthy holiday.

Sincerely,

Ronald K. Lattanze

Digitally signed by Ronald K. Lattanze
DN: cn=Ronald K. Lattanze, o=Lucerno Dynamics, LLC, ou, email=rlattanze@lucernodynamics.com, c=US
Date: 2019.12.20 11:03:56 -05'00'

Ron Lattanze
Chief Executive Officer

Enclosures:
1. Monte Carlo Simulation Report
2. Three additional extravasation cases

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

Dosimetry Validation using Monte-Carlo Simulation

Purpose: To validate the manual dosimetry method developed for radiopharmaceutical injection extravasation using Monte-Carlo simulation methods.

Method: The GATE Monte-Carlo simulation framework[1] was used to simulate absorbed dose to fixed spherical volumes over time as activity changed. Changes in simulated activity accounted for physical radioactive decay, biological clearance, and interstitial diffusion.

Cases of extravasation were chosen from our database such that various activities and tissue volumes would be represented. Simulation volumes matching the volume of initially extravasated tissue were created at one-minute intervals for 120 minutes. GATE's material definition for "muscle" (density = 1.05 g/cm^3) was used for both volumes.

At each one-minute interval, the total extravasation volume was calculated along with total activity by fitting an exponential function to the initial and PET-measured values. Activity within the initial tissue volume was calculated as a percentage of total activity based on volume. Note that for simplicity, this assumed that activity was uniformly distributed within the tissue volume.

For simulation, GATE was configured using a Dose Actor referenced to the initial tissue volume. Source activity was defined using the ion source method.

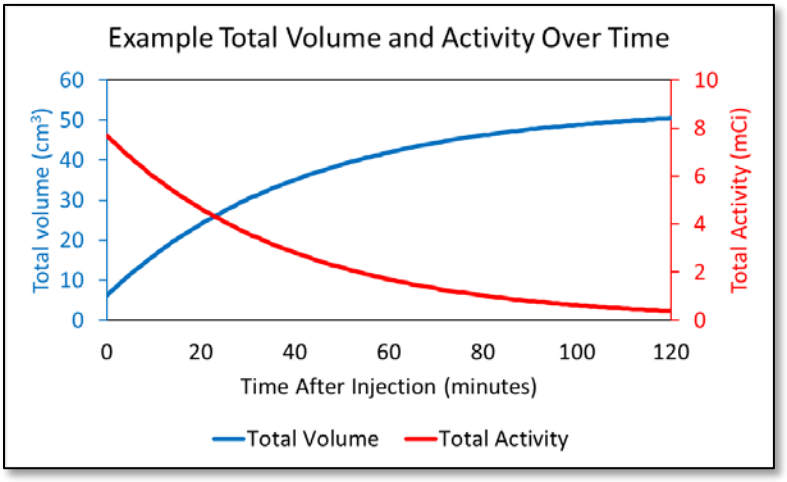


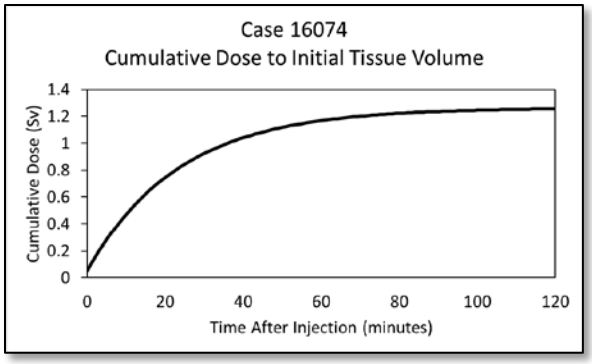
Figure 1. Example graph showing total volume and activity.

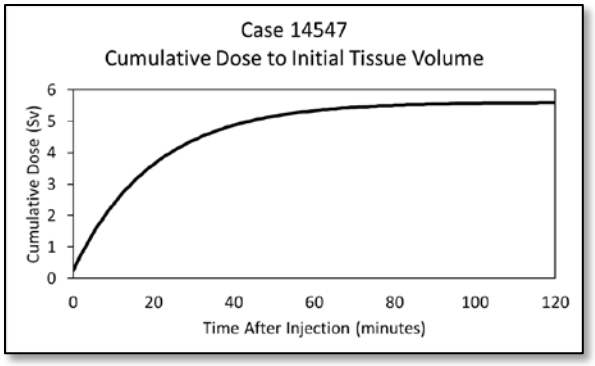
Results: For each example case, simulations were run and dose results compiled. Final results were compared to the manual dosimetry method with agreement as shown in Table 1.

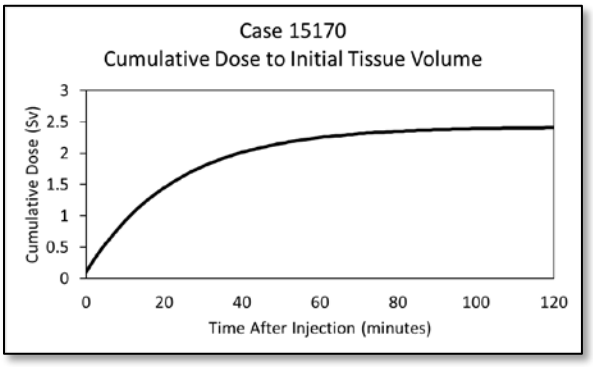
Case ID	Initial Tissue Volume (cm^3)	Manual Method Dose (Sv)	Monte-Carlo Method Dose (Sv)	Difference Between Methods
16074	1.0	1.3	1.3	3%
14547	3.0	6	5.6	7%
15170	6.2	2.6	2.4	8%

Table 1. Comparison of Dose Results for Both Methods

[1] http://www.opengatecollaboration.org/







Conclusion: In this work, we developed a Monte-Carlo method of estimating dose to infiltrated tissue that considers changes in volume and activity. The simulation method was used to validate the previously developed manual dosimetry method.

For three example cases, simulation results ranged between 3% and 8% less than the manual method. Potential sources of variability between the two methods include underlying physics assumptions as well as assumptions about the volumetric expansion of the infiltrate over time.

The manual dosimetry method uses dose rate factors from the dosimetry software IDAC Dose 2.1[2] which is itself based on Monte Carlo simulation using MCNP v6.0 with unknown physics parameters, whereas the simulations in this work used GATE v8.0 with EMStandard physics processes.

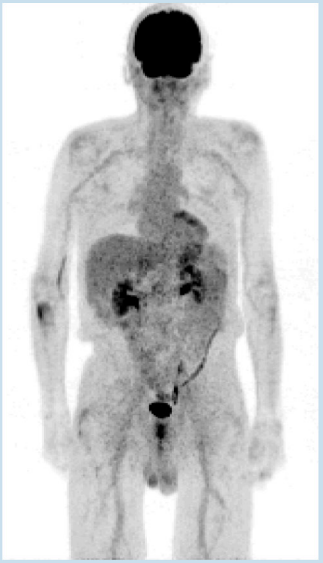
The volumetric expansion for simulation in this work was performed as an asymptotically increasing exponential function whereas the manual method uses estimated initial volume and PET-measured imaging time volumes. This difference could explain differences between the two methods.

Overall, the simulation method results confirmed that the manual method results are reasonable estimations of tissue dose. Both methods suggest these infiltrations surpass the NRC medical event reporting threshold of 500 mSv.

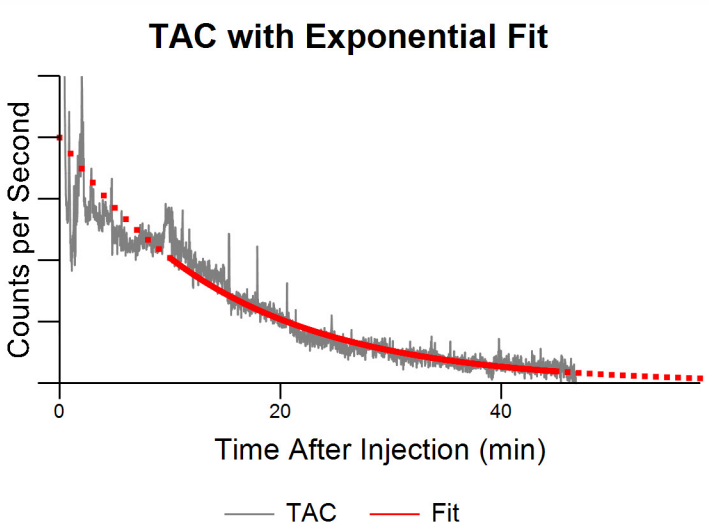
[2] Andersson M., Johansson L., Eckerman K. and Mattsson S. IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms. EJNMMI Research 2017

Scan #1010

Equivalent Dose: 0.2 to 1.2 Sv



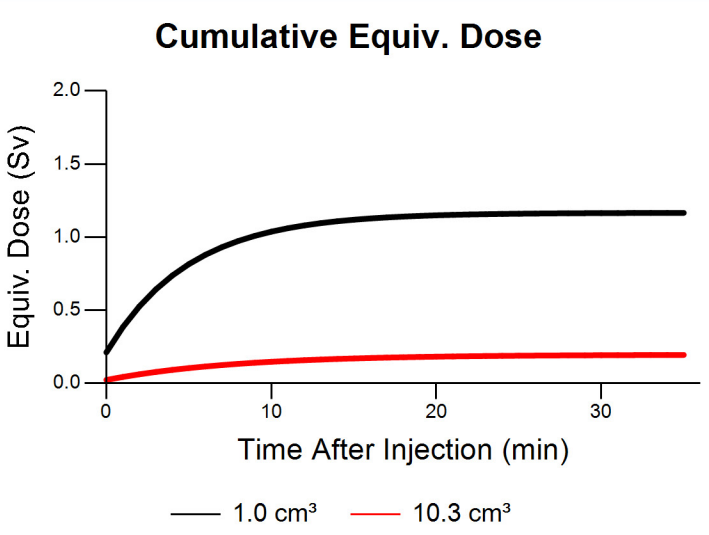
Isotope	F-18
Injection Method	Manual
Injection Location	R Antecubital
Injected Activity	14.29 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	10.0 mL
Imaging Time	56.9 min
% Extravasation	18 %
Initial Activity	2.63 mCi
Imaging Time Activity	0.04 mCi
Reabsorption Rate	10.3 min
Dose Calculation Volume	1.00 to 10.28 cm^3
Dose Rate	80.5 to 8.9 mSv/mCi-min
Total Equivalent Dose	1.2 to 0.2 Sv



As part of an 18F-FDG study, this patient was injected in the right antecubital with 14.29 mCi comprising 1.5 mL. Additionally, the injection was flushed with 10 mL of saline.

Based on PET image measurements and dynamic time-activity data, the initial infiltration was estimated to be 2.63 mCi or 18%.

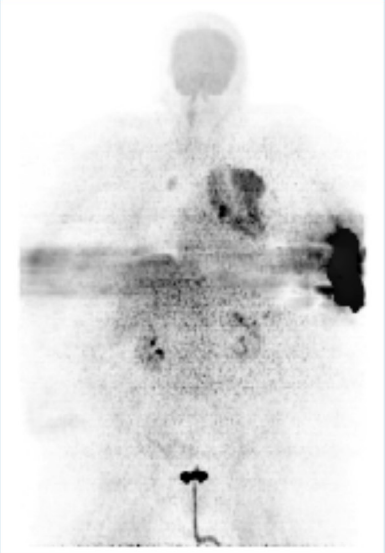
Using an initial infiltrated tissue volume of 1 cm^3, equivalent dose was calculated to be 1.2 Sv. Assuming complete infiltration of the saline flush would result in 0.2 Sv of equivalent dose to 10.28 cm^3 of tissue.



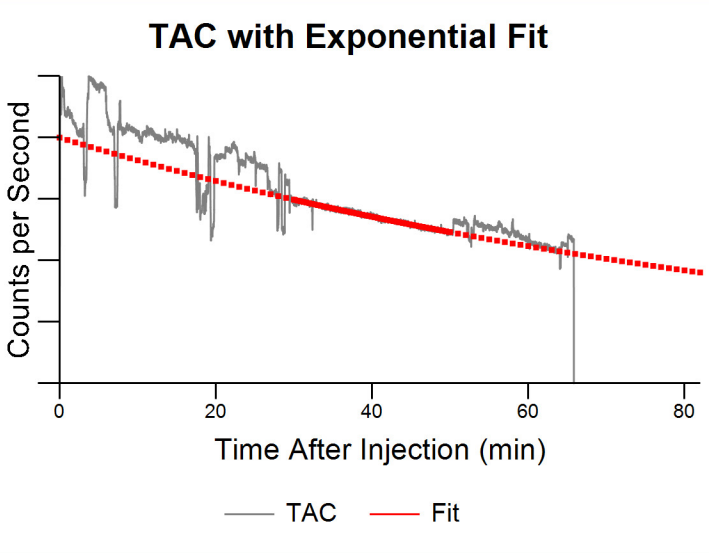
- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Scan #2078

Equivalent Dose: 1.5 to 4.9 Sv



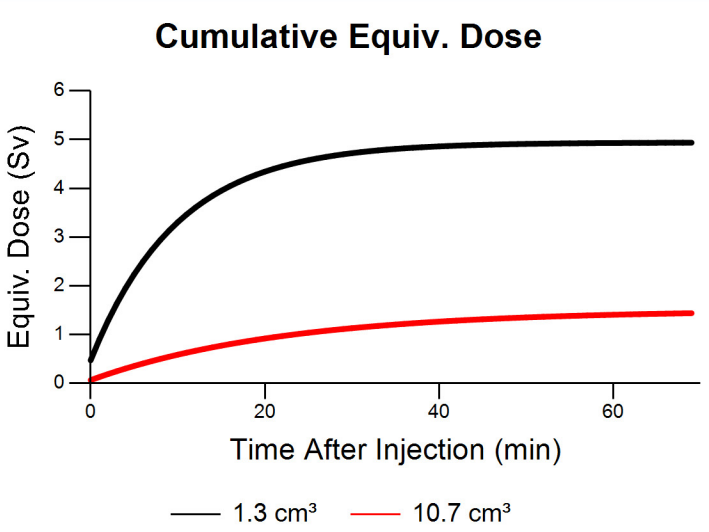
Isotope	F-18
Injection Method	Manual
Injection Location	L Antecubital
Injected Activity	17.33 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	10.0 mL
Imaging Time	76.6 min
% Extravasation	45 %
Initial Activity	7.75 mCi
Imaging Time Activity	2.27 mCi
Reabsorption Rate	71.4 min
Dose Calculation Volume	1.34 to 10.67 cm^3
Dose Rate	61.0 to 8.6 mSv/mCi-min
Total Equivalent Dose	4.9 to 1.5 Sv



The patient was injected in the left antecubital with 17.33 mCi of 18F-FDG in 1.5 mL. Subsequent flush consisted of 10 mL of saline.

At imaging time, PET measurements indicate 2.27 mCi of activity remained at the injection site, and significant image artifacts were noted.

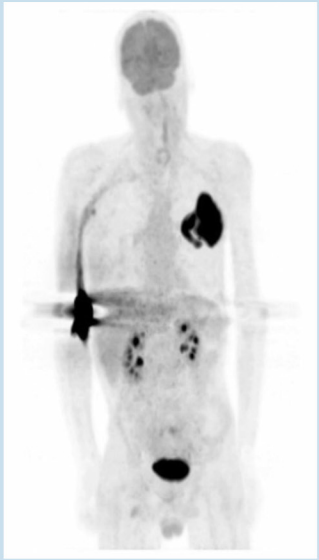
Based on PET image measurements and time-activity curve data, the initial infiltration amount was estimated to be 7.75 mCi or 45%. Equivalent dose was calculated for infiltrated tissue volumes of 1.3 cm^3 and 10.7 cm^3, and resulted in between 1.5 Sv and 4.9 Sv.



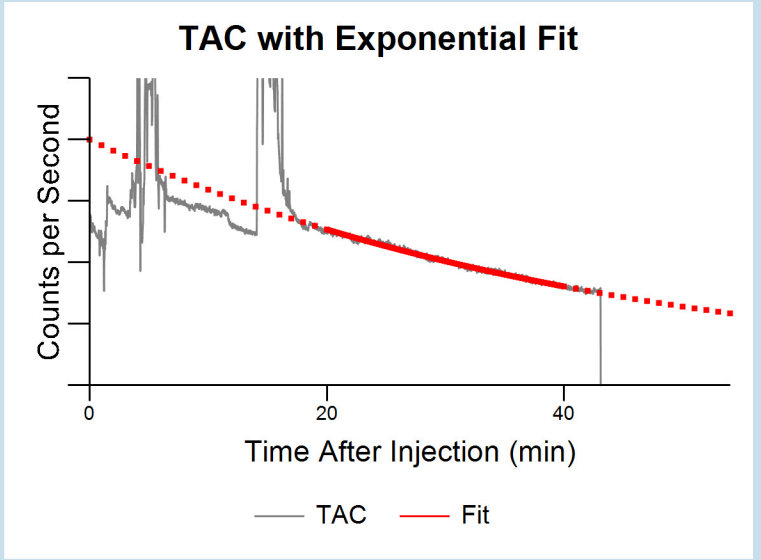
- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.

Scan #2189

Equivalent Dose: 2.4 to 5.2 Sv



Isotope	F-18
Injection Method	Manual
Injection Location	R Antecubital
Injected Activity	17.20 mCi
Radiotracer Volume	1.50 mL
Saline Flush Volume	14.0 mL
Imaging Time	61.8 min
% Extravasation	91 %
Initial Activity	15.59 mCi
Imaging Time Activity	2.59 mCi
Reabsorption Rate	30.5 min
Dose Calculation Volume	2.72 to 15.36 cm^3
Dose Rate	31.2 to 6.1 mSv/mCi-min
Total Equivalent Dose	5.2 to 2.4 Sv

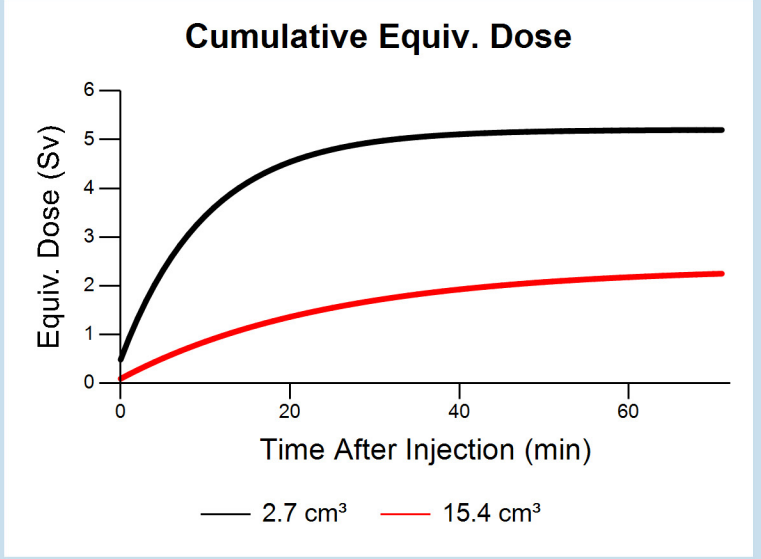


For a lung cancer imaging study, the patient was injected in the right antecubital with 17.2 mCi of FDG comprising 1.5 mL. The injection was followed by a saline flush of 14 mL. After an uptake time period of 62 minutes, PET imaging indicated 2.59 mCi remained at the injection site.

The time-activity curve indicates a reabsorption half-time of 30.5 minutes, resulting in an estimated initial infiltration of 15.6 mCi or 91%. Using the injected volumes, we calculated dose for tissue volumes of 2.70 cm^3 and 15.4 cm^3.

Dose rates for this case ranged from 31.2 mSv/mCi-min to 6.1 mSv/mCi-min and resulted in estimated doses to tissue of 5.2 Sv to 2.4 Sv.

The clinical aspects of this case have been published. doi:10.3389/fmed.2018.00143



- Dose calculation volume is twice the extravasated radiotracer volume or the total flush volume plus the extravasated radiotracer volume with a minimum volume Of 1 cm^3.
- Initial extravasation amount and reabsorption rate estimates are based on PET measurements and injection site monitoring data from Lara® sensors.
- Volumetric expansion is modeled As a mono-exponential function using initial volumes and PET measurements of volume.
- Dose rates are based on nuclear decay data from ICRP Publication 107 using the IDAC-dose 2.1 software's sphere module.