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Paper

# Practical Tools for Patient-specific Characterization and Dosimetry of Radiopharmaceutical Extravasation

Sean Wilson,[1] Dustin Osborne,[2] Misty Long,[3] Josh Knowland,[4] and Darrell R. Fisher[5]

*Abstract*—**Extravasation during radiopharmaceutical injection may occur with a frequency of more than 10%. In these cases, radioactivity remains within tissue and deposits unintended radiation dose. Characterization of extravasations is a necessary step in accurate dosimetry, but a lack of free and publicly available tools hampers routine standardized analysis. Our objective was to improve existing extravasation characterization and dosimetry methods and to create and validate tools to facilitate standardized practical dosimetric analysis in clinical settings. Using Monte Carlo simulations, we calculated dosimetric values for sixteen nuclear medicine isotopes: $^{11}$C, $^{64}$Cu, $^{18}$F, $^{67}$Ga, $^{68}$Ga, $^{123}$I, $^{131}$I, $^{111}$In, $^{177}$Lu, $^{13}$N, $^{15}$O, $^{82}$Rb, $^{153}$Sm, $^{89}$Sr, $^{99m}$Tc, and $^{90}$Y. We validated our simulation results against five logical alternative dose assessment methods. We then created three new characterization tools: a worksheet, a spreadsheet, and a web application. We assessed each tool by recalculating extravasation dosimetry results found in the literature and used each of the tools for patient cases to show clinical practicality. Average variation between our simulation results and alternative methods was 3.1%. Recalculation of published dosimetry results indicated an average error of 7.9%. Time required to use each characterization tool ranged from 1 to 5 min, and agreement between the three tools was favorable. We improved upon existing methods by creating new tools for characterization and dosimetry of radiopharmaceutical extravasation. These free and publicly available tools will enable standardized routine clinical analysis and benefit patient care, clinical follow-up, documentation, and event reporting.**

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**Key words: dosimetry; medical radiation; nuclear medicine; radiopharmaceuticals**

## BACKGROUND

RADIOPHARMACEUTICALS ARE typically administered to patients through intravenous injection or infusion. As previously reported, diagnostic radiopharmaceutical extravasation may occur with a frequency of more than 10%[6] (Hall et al. 2006; Bains et al. 2009; Krumrey et al. 2009; Osman et al. 2011; Silva-Rodriguez et al. 2014; Muzaffar et al. 2017; Wong et al. 2019; Currie and Sanchez 2020). Extravasations degrade diagnostic images (Slavin et al. 1996; Fleming et al. 2004; Naddaf et al. 2004; Burrell and MacDonald 2006; Waxman et al. 2009; Murray et al. 2013; Ozdemir et al. 2014; Minoshima et al. 2016; QIBA SPECT Biomarker Committee 2017; Erthal et al. 2017; Schaefferkoetter et al. 2017; van der Pol et al. 2017; Bennett et al. 2018; Kiser et al. 2018; Murthy et al. 2018; Qutbi 2018) and cause unintentional radiation dose to the patient's tissue and skin. Prompt identification of potentially serious extravasations is important for mitigation (e.g., massage, elevation). Characterization and dosimetry are then necessary to inform long-term patient care, clinical follow-up, event documentation, and reporting as applicable.

Tissue-absorbed dose resulting from extravasation depends on patient- and procedure-specific factors including the initial amount of paravenous radioactivity, the mass of infiltrated tissue, the radiopharmaceutical used, and residence time. For example, the length of time that extravasated radiopharmaceutical remains near the injection site can depend on the patient's anatomy, vascular health, and properties of the drug, such as the rate at which it is able to permeate interstitial space. Likewise, the volume of infiltrated tissue can vary with administration technique; for instance, use of a straight stick needle for injection as opposed to an intravenous catheter precludes flushing with saline and thus limits dilution and dispersion of residual radioactivity. Because the amount of extravasated radioactivity and the volume of infiltrated tissue both change over time, conventional static nuclear

[1]Carilion Clinic, Roanoke VA and Blue Ridge Medical Physics, Daleville, VA; [2]University of Tennessee Graduate School of Medicine, Knoxville TN; [3]Siemens Medical Solutions, Knoxville TN; [4]Lucerno Dynamics, Cary NC; [5]University of Washington Department of Radiology and Versant Medical Physics and Radiation Safety, Richland, WA.

The authors declare no conflicts of interest.

For correspondence contact: Josh Knowland, 140 Towerview Ct., Cary, NC 27513, or email at **jknowland@lucernodynamics.com**.

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[6]McIntosh C, Abele J. Frequency of interstitial radiotracer injection for patients undergoing bone scan. The 79th Annual Scientific Meeting of the Canadian Association of Radiologists. Montreal, Canada. 2016.

medicine imaging by itself can be an inadequate tool for dosimetry characterization. Serial imaging of the injection site or monitoring with nuclear uptake probes have been proposed as improved ways to inform characterization (Breen and Dreidger 1991; Williams et al. 2006; Bonta et al. 2011; Terwinghe et al. 2012; Kawabe et al. 2013; Esser 2017; Tylski et al. 2018).

Even with measurements from serial imaging or uptake probes, extravasation dosimetry requires effort to determine appropriate dose rates and clearance times. A recent publication (Osborne et al. 2021) proposed pre-calculated dose rates for a standardized tissue volume of 5 $cm^3$—a tissue volume also used by others (Castronovo et al. 1988; Narkevich et al. 2019)—in analysis of radiopharmaceutical extravasations. The method uses injection-site radioactivity measurements to estimate the rate of biological clearance and is applicable to clinical extravasation characterization and dosimetry.

In this work, we built upon the efforts of Osborne et al. (2021) by pre-calculating dosimetric data for several additional isotopes. We then created and validated three free and publicly available tools for characterization and dosimetry of extravasations to facilitate routine use, standardization, and conformity.

## MATERIALS AND METHODS

We calculated dose rates for sixteen common nuclear medicine isotopes: $^{11}C$, $^{64}Cu$, $^{18}F$, $^{67}Ga$, $^{68}Ga$, $^{123}I$, $^{131}I$, $^{111}In$, $^{177}Lu$, $^{13}N$, $^{15}O$, $^{82}Rb$, $^{153}Sm$, $^{89}Sr$, $^{99m}Tc$, and $^{90}Y$. These data were generated using Monte Carlo simulations of 5 $cm^3$ water-filled spherical volumes each containing a uniformly distributed activity of 100 kBq. Simulations were run using version 9.1 of the GATE Monte Carlo framework (Jan et al. 2004). Within GATE, source isotopes were defined by their characteristic ionic forms. Ionic sources represent an accurate source type within GATE because they incorporate all emissions and nuclear processes, including ingrowth and decay of progeny products, as applicable. Simulated events within each of the 5 $cm^3$ volumes were generated, recorded, and analyzed to determine the energy deposited per nuclear transition.

To validate the Monte Carlo simulations, we compared our results against five alternative dose-assessment methods that represent logical approaches one may take. The first alternative method was the IDAC-Dose 2.1 software version 1.04 (Andersson et al. 2017), which is freely available and endorsed for radiopharmaceutical dosimetry by the International Commission on Radiological Protection (ICRP). We used the "spheres" module within IDAC-Dose to calculate absorbed dose to spherical volumes. The second method we employed was the sphere dose calculation function of OLINDA® version 2.2.3 (Hermes Medical Solutions, Stockholm, Sweden). For consistency of comparison against the Monte Carlo simulations, both IDAC-Dose and OLINDA were configured to calculate dose resulting from 100 kBq within water-filled spheres of mass 5 g. The third alternative method consisted of a Monte Carlo simulation using discrete emissions. The fourth method was a simplification of the third and used only one emission of each type with energy equal to the weighted average of their respective constituents. For example, electron and positron emission energies were summed according to their individual yield intensities and were then represented by one electron of equivalent energy. Likewise, all photons were represented using a weighted average of their underlying emissions. Finally, the fifth alternative method assumed complete absorption of non-penetrating emissions and no absorption of penetrating emissions.

We created three new extravasation characterization and dosimetry tools: a manual worksheet, a computer spreadsheet, and an online web application. We validated each of the tools through recalculation of and comparison against three previously reported examples of extravasation dosimetry (Castronovo et al. 1988).

To determine clinical practicality of the tools, we applied them to seven cases of diagnostic nuclear medicine extravasation and recorded the time required for each characterization. At our institutions, we routinely monitor nuclear medicine injections and record injection site count-rate data throughout the pre-imaging uptake time using Lara® external uptake probes (Lucerno Dynamics, Cary, NC). When probe feedback indicated possible extravasation, technologist staff would include the injection site in the imaging field-of-view. We performed quantitative image-based activity measurements using syngo®.via version 6.5 (Siemens Healthineers AG, Erlangen, Germany) with volumes of interest (VOIs) centered about the maximal local voxel and defined by a 10% threshold value.

## RESULTS

Tables 1 and 2 show dose factors and mean absolute percent error values, respectively, for the six calculation methods. Table 3 compares doses obtained using each of the characterization tools against published values (Castronovo et al. 1988). Table 4 shows the results of characterization for clinical cases of extravasation.

## DISCUSSION

In this work, we developed three tools for characterization and dosimetry of radiopharmaceutical extravasations. We validated all three tools against published data and demonstrated their practicality within a clinical workflow. All three tools are available at no charge online[7] or from the authors.

[7]Radiopharmaceutical Infiltration Dosimetry Estimator (RIDE), http://gsm.utmck.edu/research/MITRP/RIDE.cfm. Accessed 26 April 2022.

**Table 1.** Self-dose factors (mGy/MBq) for six different calculation methods.

| Isotope | Ion Source Simulation | IDAC-Dose 2.1 | OLINDA 2.2.3 | Discrete Emission Simulation | Weighted Average Emission Simulation | Non-Penetrating Emissions Only |
|---|---|---|---|---|---|---|
| C-11 | 21.8 | 21.8 | 22.1 | 23.6 | 22.1 | 20.3 |
| Cu-64 | 267.8 | 266.8 | 268.0 | 278.7 | 270.3 | 255.9 |
| F-18 | 78.7 | 78.3 | 79.0 | 87.6 | 78.4 | 70.8 |
| Ga-67 | 584.3 | 576.3 | 536.0 | 579.9 | 518.1 | 478.3 |
| Ga-68 | 120.2 | 120.9 | 126.0 | 129.9 | 126.9 | 116.0 |
| I-123 | 78.1 | 78.3 | 77.2 | 78.2 | 70.9 | 61.8 |
| I-131 | 6,276.0 | 6,268.5 | 6,330.0 | 6,414.7 | 6,384.5 | 5,986.1 |
| In-111 | 545.1 | 543.4 | 538.0 | 543.6 | 507.9 | 385.0 |
| Lu-177 | 3,871.2 | 3,880.5 | 3,940.0 | 3,905.0 | 3,958.6 | 3,843.1 |
| N-13 | 13.1 | 13.1 | 13.4 | 14.1 | 13.3 | 12.3 |
| O-15 | 3.7 | 3.7 | 3.9 | 4.0 | 3.8 | 3.5 |
| Rb-82 | 3.6 | 3.6 | 3.8 | 3.9 | 3.9 | 3.5 |
| Sm-153 | 2,045.3 | 2,042.1 | 2,030.0 | 2,076.6 | 2,045.4 | 2,023.0 |
| Sr-89 | 105,833.4 | 103,405.0 | 108,000.0 | 109,467.2 | 108,543.8 | 105,799.6 |
| Tc-99m | 19.6 | 19.4 | 19.6 | 19.4 | 18.8 | 16.2 |
| Y-90 | 8,075.2 | 7,971.8 | 8,530.0 | 8,569.8 | 8,528.5 | 8,072.2 |

Dose rates from our simulations compared favorably with alternative methods of calculation. Differences between our simulation of ion sources and alternative calculation methods one through four (IDAC-Dose 2.1, OLINDA 2.2.3, simulation of discrete emissions, and simulation of weighted average emissions) were all less than 4%. With respect to the OLINDA dosimetry software, it is important to point out that recent code updates have improved the spheres module performance. For this work, agreement between OLINDA and the other calculation methods was poor until the software was updated to version 2.2.3. The difference between our ion simulations and an assumption of complete absorption of non-penetrating emissions only (alternative calculation method five) was almost 10%. This assumption may be considered naïve but has been previously proposed as a solution (Shapiro et al. 1987) with the reasoning that for relatively small volumes, the absorbed fraction for photons will tend to be insignificant compared to that of electrons. This simplification can lead to significant bias. In our simulation of $^{18}$F, only 2.6% of the emitted annihilation photon energy was deposited within the 5 cm$^3$ sphere, but this photon energy accounted for 10% of the total energy deposited. An assumption of no photon absorption resulted in an underestimate of overall absorbed energy.

**Table 2.** Mean absolute percent error for alternative dose rate methods as compared to ion source simulation.

| Calculation method | Error |
|---|---|
| IDAC-Dose 2.1 | 0.29% |
| OLINDA 2.2.3 | 1.06% |
| Discrete Emission Simulation | 3.96% |
| Weighted Average Emission Simulation | 0.11% |
| Non-Penetrating Emissions Only | 9.83% |

Application of the characterization tools to a clinical workflow showed that the tools have practical value and can be used within a normal clinical setting. Characterization and dosimetry required, on average, between 8 and 15 min—of which only 1 to 5 min were in addition to actions already recommended by medical guidelines for cases of extravasation (Boellaard et al. 2015). At our institutions, we routinely monitor radiopharmaceutical injections using high temporal-resolution uptake probes. This practice simplifies characterization, but other data collection methods may also be appropriate. For example, periodic measurement with a mobile ion chamber (Berry and Kendrick 2022) or serial imaging of the injection site, depending on the availability of technology and personnel, would be obvious options. We used syngo.via for quantitative image analysis because of availability and our own experience, but we would expect software from other vendors to produce comparable results.

Dosimetry results from each of the three characterization tools indicated favorable agreement. We analyzed the results statistically for significant differences and relationships. Data were indicated to be within normality standards and of equal variance. Pearson correlation coefficients between groups were greater than 96% with $P < 0.001$. No statistical difference was detected between groups by one-way ANOVA

**Table 3.** Results for recalculation of work published by Castronovo et al. (1988) (absorbed dose, Gy).

| Isotope | Castronovo et al. | Worksheet | Spreadsheet | Web Application |
|---|---|---|---|---|
| $^{99m}$Tc Microspheres | 1.78 | 1.70 | 1.69 | 1.78 |
| $^{99m}$Tc MDP | 2.74 | 2.28 | 2.96 | 2.42 |
| $^{67}$Ga Citrate | 1.65 | 1.50 | 1.83 | 1.74 |

**Table 4.** Results of characterization for clinical cases of extravasation.

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
|---|---|---|---|---|---|---|---|
| Isotope | $^{18}$F | $^{18}$F | $^{68}$Ga | $^{18}$F | $^{18}$F | $^{18}$F | $^{18}$F |
| Administered activity (MBq) | 473.6 | 525.4 | 180.6 | 606.4 | 481.4 | 355.2 | 395.9 |
| Image-based activity measurement (MBq) | 20.8 | 85.2 | 19.1 | 19.0 | 137.1 | 13.1 | 4.8 |
| Time between injection and imaging (min) | 68.9 | 79.0 | 78.3 | 78.5 | 60.6 | 65.0 | 53.0 |
| Effective half-life (min) | 27.2 | 40.8 | 34.7 | 53.9 | 55.3 | 25.8 | 40.3 |
| Tissue absorbed dose, Worksheet (Gy) | 2.0 | 16.2 | 5.1 | 3.0 | 17.6 | 1.2 | 0.38 |
| Tissue absorbed dose, Spreadsheet (Gy) | 4.3 | 16.7 | 7.9 | 3.2 | 17.3 | 1.3 | 0.39 |
| Tissue absorbed dose, Web Application (Gy) | 2.7 | 17.4 | 7.0 | 2.6 | 13.4 | 1.6 | 0.39 |

($F = 0.035$, $P = 0.966$). A Tukey post-hoc analysis confirmed no statistically significant difference in means with $P > 0.97$ for all comparisons.

For image-based activity measurements, we used VOIs defined using a threshold of 10% of local maximum and relied on multiplication of average enclosed activity (Bq mL$^{-1}$) by volume (cm$^3$). This approach may underestimate the residual activity because in cases of extravasation, even 10% of the maximal voxel's value can be significantly higher than background. However, the potential loss of accuracy is offset by a reduction in effort and complexity. We expect that a larger number of VOI segments would result in increased accuracy but decreased utility.

Osborne et al. (2021) previously reported that for cases of radiopharmaceutical extravasation, deep tissue dose can be significantly higher than dose to overlying skin. Additionally, appropriate tools already exist for the complex task of skin dosimetry (e.g., VARSKIN) (Hamby and Mangini 2018). For these reasons, we chose instead to concentrate only on calculation of tissue absorbed dose.

We acknowledge that the set of radionuclides included in this work is not exhaustive and does not include, for example, therapeutic alpha emitters. Although extravasation of alpha emitting radiopharmaceuticals can be serious (Benjegerdes et al. 2017; Frantellizzi et al. 2020), dosimetry for these cases would involve assumptions different from those made in this work (e.g., the degree of equilibrium, biodistribution of radioactive progeny over time). The radionuclides presented in this work encompass most nuclear medicine procedures, but we do anticipate the creation of tools to enable straightforward characterization and dosimetry of additional use cases.

## CONCLUSION

Accurate extravasation dosimetry requires characterization of the event. In this work, we developed three extravasation characterization and dosimetry tools, validated each against published data, and demonstrated their utility in a realistic clinical workflow. Free and publicly available tools for practical and rapid characterization of extravasations will be beneficial to patient care, clinical follow-up, documentation, and event reporting.

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